Sugar Silanes: Versatile Reagents for Stereocontrolled Glycosylation via Intramolecular Delivery

by

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Dedication

To my mother and my grandparents. Without their strength, character, and support, I could never have accomplished the things that I have.

Acknowledgments

First and foremost, I am most grateful for my family. I have been surrounded by incredible people my entire life. It was only with your love that I have achieved what I have. My success is your success.

John Montgomery has provided wonderful guidance and mentorship as my career has developed. I'd also like to thank John Wolfe, Pavel Nagorny, Amanda Garner, and Jason Gestwicki for their insights into the sugar silane project.

I've had the great pleasure of working next to wonderful people in the Montgomery Lab. More than coworkers, these friends have enriched my life and helped to create memories that I will always cherish.

Last but not least, I love Kelli Sullivan with all of my heart.

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°C	Degrees Celcius
Å	Angstrom
Ac	Acetyl
AIDS	Acquired Immune Deficiency Syndrome
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
COD	Cyclooctadiene
CSA	Camphorsulphonic Acid
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-Dicyano-1,4-Benzoquinone
DMF	Dimethylformamide
DMTST	Dimethylsulfonium Triflate
DNA	Deoxyribonucleic Acid
DTBMP	2,6-Di-*Tert*-Butyl-4-Methyl-Pyridine
Equiv	Equivalent(s)
Et	Ethyl
HIV	Human Immunodeficiency Virus
HRMS	High Resolution Mass Spectroscopy
IAD	Intramolecular Aglycone Delivery
Icy	1,3-bis(cyclohexyl)-imidazolium
IDCT	Iodonium Dicollidine Triflate

IMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IPr	1,3-bis(2,6-diisopropylphenyl)-imidazolium
LG	Leaving Group
Me	Methyl
MS	Molecular Sieves
NHC	*N*-Heterocyclic Carbene
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
PG	Protecting Group
Ph	Phenyl
Phth	Phthalimide
PMB	*para*-methoxybenzyl
Pr	Propyl
Quant.	Quantitative
SIMes	1,3-bis(2,4,6-trimethylphenyl)-imidazolinium
S_N1	Unimolecular Nucleophilic Substitution
S_N2	Bimolecular Nucleophilic Substitution
TBAF	Tetrabutylammonium Fluoride
TBS	Tributylsilyl
Tf	Triflate
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Tr	Trityl
Ts	Tosylic

Abstract

Carbohydrates play many roles in the complex biological systems found within Nature. An important goal in carbohydrate chemistry is the development of diastereoselective glycosylation methods to incorporate carbohydrates in an expedient and high yielding fashion. Intramolecular glycosylation is an approach whereby a glycosyl donor and acceptor are tethered together and subsequent activation of the donor results in diastereoselective transfer of the aglycone to the anomeric position. Previous work in the Montgomery group has focused on the development of carbohydrate-bearing silane reducing agents termed "sugar silanes." Using these reagents, the direct reductive glycosylation of carbonyl substrates and the three-component assembly of glycosylated products via the catalytic union of aldehydes, alkynes, and sugar silanes is possible. We now describe a new method for the dehydrogenative silylation of alcohols using sugar silanes followed by intramolecular glycosylation. Appropriate combinations of silane position and protecting group allow highly selective access to β-manno, α-gluco, or β-gluco stereochemical relationships as well as β-2-azido and β-2-deoxyglycosides. Expanding upon the more traditional tethering at the C2 hydroxyl of the donor, the C6 hydroxyl is utilized for tethering to give the first general method to obtain 1,2-*trans* glycosides via intramolecular aglycone delivery.

Chapter 1

Carbohydrate Chemistry

1.1) General Overview of Carbohydrates

The World Health Organization (WHO) estimates that communicable diseases (respiratory infections, HIV/AIDS, diarrheal diseases) are the leading causes of death in low-income countries, while the majority of deaths in high-income countries are due to non-communicable diseases (cardiovascular disease, cancer, neurological conditions).[1] Increased scientific knowledge continues to improve our ability to diagnose, treat, and prevent a wide variety of diseases. The success of chemotherapeutics, along with a better understanding of glycobiology, has increased the demand for carbohydrate-based therapeutic agents.[2,3,4] However, the utilization of carbohydrates for the benefit of mankind has a storied tradition which stretches back millennia.

The unique properties of carbohydrates have been recognized by humanity since before the development of written history. The first record of honey collection is found in cave paintings near Valencia, Spain and date back at least 8,000 years.[5] Beekeeping is depicted in ancient Egyptian hieroglyphics.[6] Sugar cane has been cultivated as an important cash crop for millennia. The need for better regulation of the sugar industry during the 19th century led to a desire for an improved understanding of carbohydrate

structure. However, it wasn't until late in the century that the basic tenets of organic chemistry were uncovered to provide a framework for this knowledge.

Carbohydrate chemistry and organic chemistry share a symbiotic past. Despite the difficulty of obtaining poorly recrystallizing carbohydrates as pure samples, they were some of the most heavily studied organic compounds in the late 19th century. It was Emil Fischer's work on the relative configuration of carbohydrates that confirmed the van't Hoff-Le Bel theory of tetrahedral saturated carbons.[6] The importance of this work cannot be overstated. Jacobus van't Hoff won the inaugural Nobel Prize in Chemistry in 1901, only to be followed by Emil Fischer the following year.

Carbohydrates gained their name due to a molecular formula of $C_n(H_2O)_n$. This formula corresponds to the "hydrate of carbon." Carbohydrates are now recognized to include a diverse array of compounds, all of which consist of or are derived from aliphatic polyhydroxyl ketones or aldehydes. Carbohydrates also contain several chiral centers which add to their structural complexity. Glucose and mannose, two carbohydrates isomers, differ by the inversion of one stereocenter (Figure 1.1).

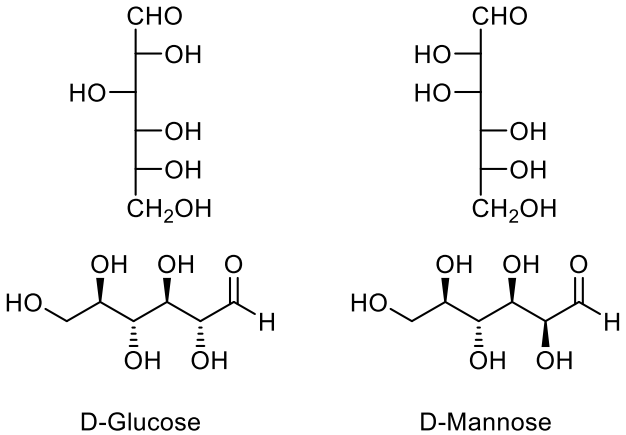
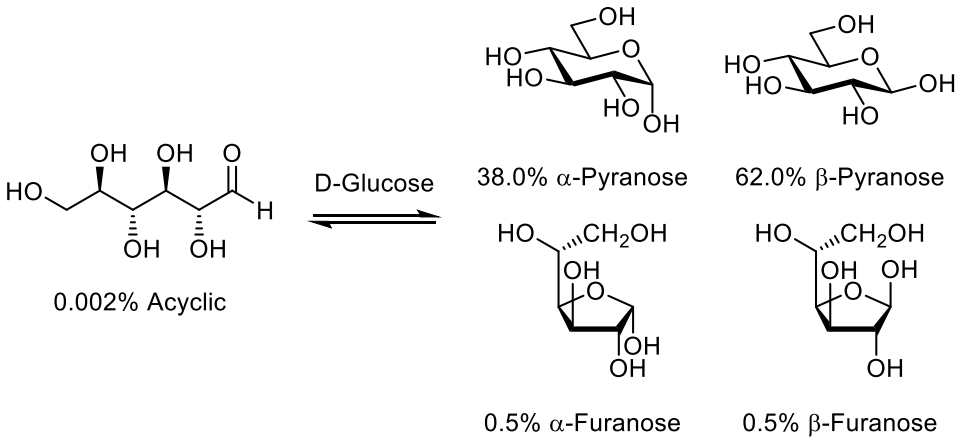


Figure 1.1 – D-Glucose and D-Mannose

As carbohydrates contain both the nucleophilicity of alcohols and the electrophilicity of carbonyls, they are able to react intramolecularly to form cyclic hemiacetals. A variety of ring sizes are possible, however five and six membered rings are by far the most common.[6] A new chiral center is formed at the carbonyl and is identified as the anomeric carbon. When they are dissolved in solution, carbohydrates undergo mutarotation, an equilibrium process involving different ring sizes and different anomeric stereochemistry. After approximately three hours in solution, D-Glucose exists as a variety of isomers (Scheme 1.1).[6]



Scheme 1.1 – Mutarotation of Glucose

One of the principles of first semester organic chemistry is that the substituents of a cyclohexane ring influence the preferred chair conformation due to 1,3-diaxial interactions. For thermodynamic reasons, the cyclohexane ring will favor a conformation where bulkier substituents are in an equatorial position. Considering that mutarotation is an equilibrium process, it is at first glance surprising to see that the pyranose isomer of D-glucose exists as an anomeric mixture of 38:62 α:β. The hydroxyl at the anomeric position would be expected to more highly favor the equatorial, or β, position. This

unexpected result was first observed by Edwards[7] and later named the "anomeric effect" by Lemieux.[8] A topic of continuing academic conversation, there are two explanations that are widely accepted to explain the anomeric effect (Figure 1.2).[6] First, the axial orientation minimizes dipole-dipole interactions between the anomeric carbon-pyran oxygen bond and the anomeric carbon-exocyclic oxygen bond. Secondly, the axial orientation provides a σ* orbital which a pyran oxygen lone pair can donate into through a hyperconjugative effect.

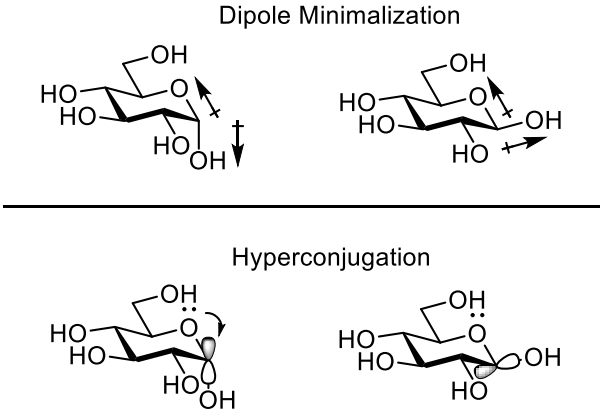


Figure 1.2 – The Anomeric Effect

Monosaccharide subunits can combine to form di- and oligosaccharides. For example, glucose and fructose can undergo a condensation reaction to form sucrose, or table sugar (Figure 1.3). The difference between the glycans of glycoconjugates on the surface of red blood cells is in part the reason that humans have different blood types. Oligosaccharides can display astounding complexity due to the potential branched products that can form. Using only the known naturally occuring monosaccharides, it has been estimated that there are 192,780,943,360 possible hexasaccharides.[9]

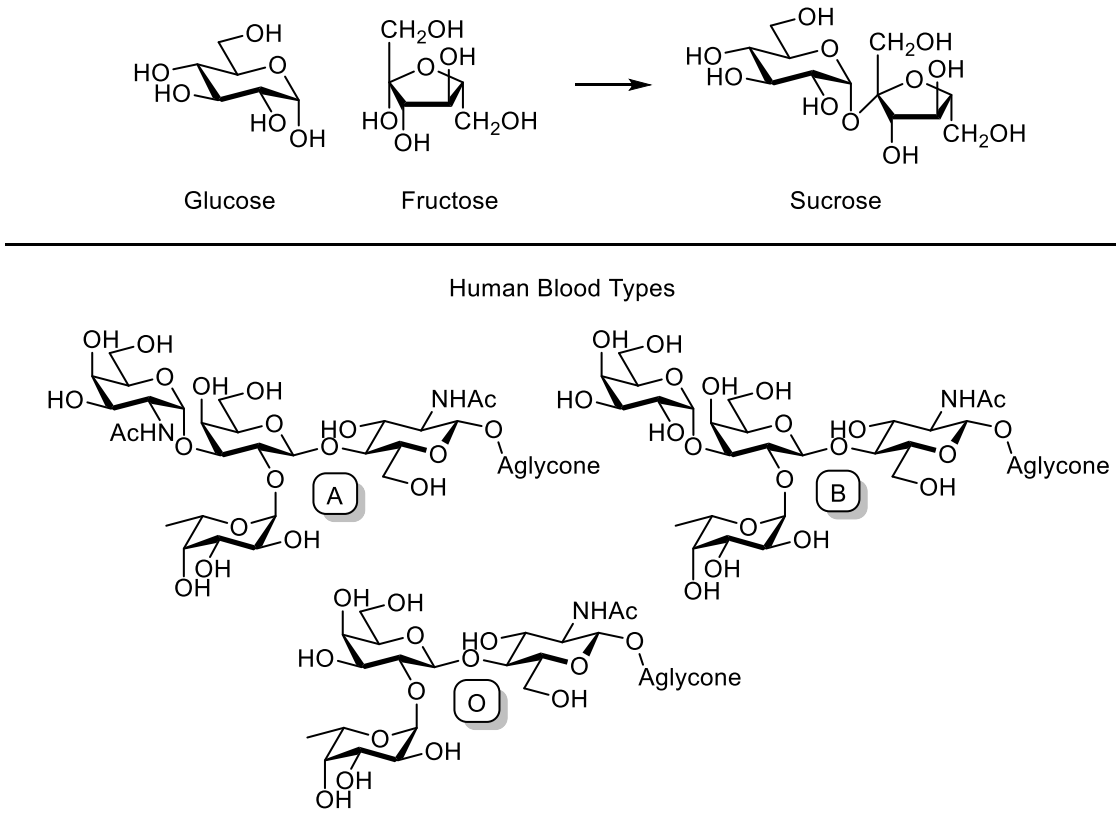


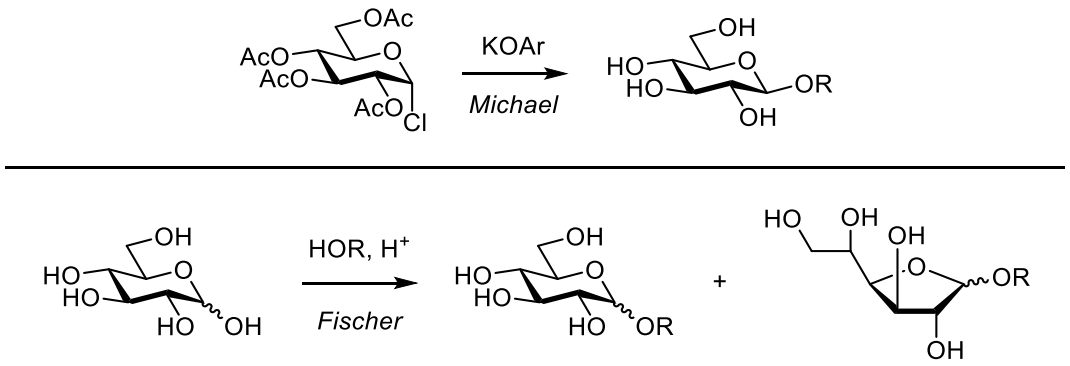
Figure 1.3 – Disaccharides and Oligosaccharides

The majority of naturally occurring carbohydrates exist as polysaccharides, glycoconjugates, or glycosides, whereby a glycoside unit is attached to an aglycone through a glycosidic bond.[10] Glycans attached to cell surfaces, proteins, and lipids mediate the biological function of biomolecules and are essential to glycoprotein folding, cellular homeostasis, and immune regulation.[11] Furthermore, glycans have been shown to play a role in a variety of diseases, including cancer.[12] Unfortunately, it can often be difficult to isolate pure samples of glycans and despite being cell-type specific, many glycans have no known benefit.[13] In addition to the natural complexity of carbohydrates, the study of the glycome is further hindered by the fact that it is not genetically encoded but is the result of a variety of regulatory processes.[14]

New breakthroughs in glycochemistry and glycobiology have provided a better understanding of the role that glycans play in a variety of biological processes and has driven research towards the development of novel carbohydrate-based therapeutics.[15] The interest in these new therapeutics has increased the demand for synthetic routes to highly functionalized glycoconjugates. Despite this demand, the lack of general methods continues to attract synthetic chemists towards this challenge of developing efficient and stereoselective strategies to install carbohydrates.[10,16,17,18]

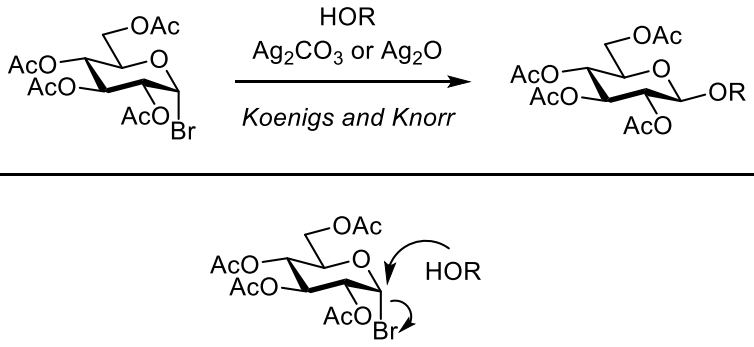
1.2) Development of Glycosylation Strategies

American chemist Arthur Michael, known primarily for the discovery of the Michael reaction[19], reported the first example of a chemical glycosylation in 1879.[20] Despite a relative lack of knowledge regarding the structure and reactivity of carbohydrates, Michael found that the potassium salts of aryl alcohols are able to react with anomeric chlorides to give new glycosides (Scheme 1.2). While unknown at the time, the glycosylation was later shown to favor the inversion of stereochemistry at the anomeric center due to an S_N2 mechanism. Over a decade later, Fischer reported a new glycosylation method which takes advantage of the cyclic hemiacetal nature of carbohydrates. He found that treating glucose to harshly acidic conditions in the presence of excess alcohol results in the formation of multiple species including anomeric mixtures of both the pyranoside and the furanoside (Scheme 1.2).[21,22] An important lesson from the Fischer glycosylation method was that the use of alcohol protecting groups is necessary to prevent interconversion between five-membered and six-membered rings during glycosylations.



Scheme 1.2 – First Chemical Glycosylations by Michael and Fischer

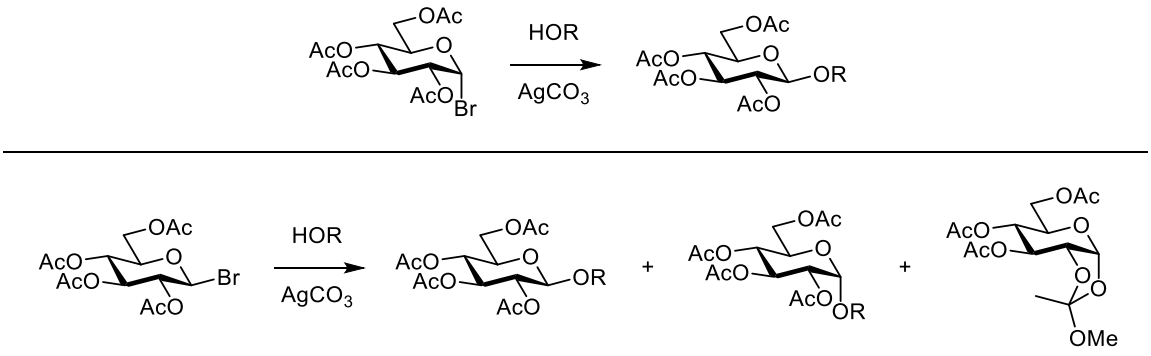
In 1901, Koenigs and Knorr reported that the treatment of 1,2-*cis* glycosyl bromides with silver carbonate or silver oxide in the presence of an alcohol gives newly formed glycosidic bonds (Scheme 1.3).[23] It was noted that the reaction proceeds with good stereoselectivity and that it favors inversion of the anomeric center. With limited knowledge of glycosylation mechanisms at the time, it was rationalized that the reaction proceeds through a concerted nucleophilic substitution to give the inverted product.



Scheme 1.3 – Koenigs-Knorr Glycosylation and Proposed Mechanism

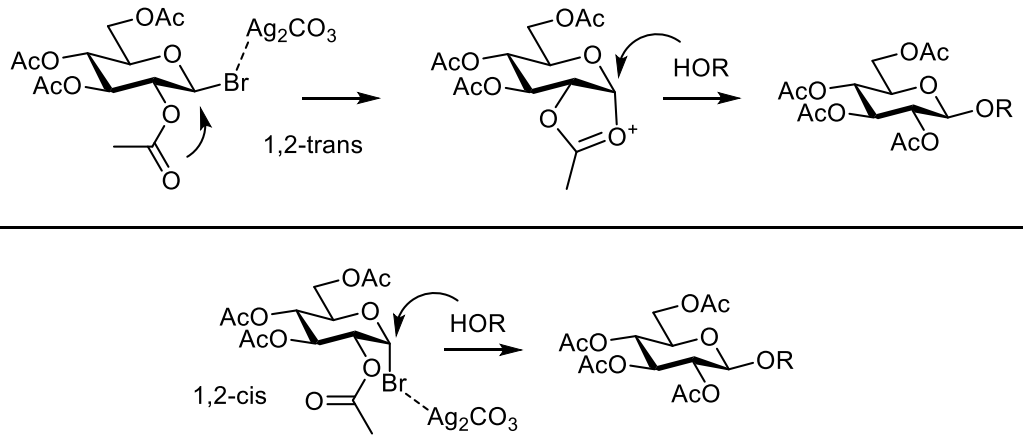
Later work by Isbell showed that there is a difference in the reactivity of 1,2-*cis* and 1,2-*trans* glycosyl bromides (Scheme 1.4).[24,25] He confirmed that the Koenigs-Knorr glycosylation proceeds with inversion using 1,2-*cis* glycosyl bromides. However, the reaction of 1,2-*trans* glycosyl bromides under the same conditions results in the

formation of three products: the α-glucoside, the β-glucoside, and the 1,2-orthoester resulting from nucleophilic attack by the C2-acetoxy group. The formation of the 1,2-orthoester is a strong indicator that the neighboring C2-acetoxy group is involved in the mechanism. Rate studies by Winstein showed that C2-acetoxy participation in the mechanism greatly lowers the transition state energy versus the formation of a free oxocarbenium cation through the unassisted departure of the bromide leaving group.[26,27]



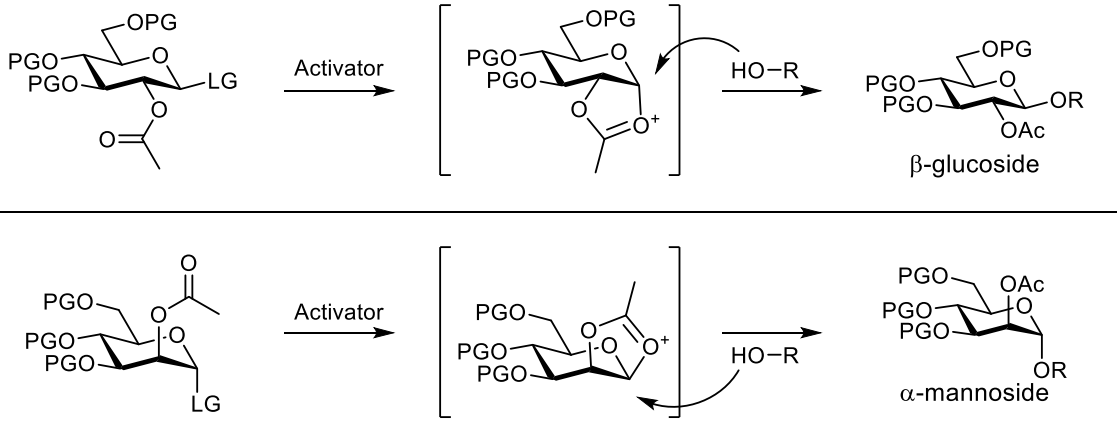
Scheme 1.4 – Different Reactivity Between 1,2-*Cis* and 1,2-*Trans* Donors

These contributions eventually led Isbell to propose two different mechanisms by which 1,2-*trans* and 1,2-*cis* glycosyl bromides are activated (Scheme 1.5). 1,2-*Trans* glycosyl bromides likely proceed through a fast C2-acetoxy assisted reaction mechanism which result in the formation of multiple products. The lack of 1,2-orthoester byproducts in the reaction involving 1,2-*cis* glycosyl bromides indicates a slower concerted nucleophilic displacement. This is now recognized as one of the few glycosylation procedures that proceed through an intermolecular S_N2 pathway.[28]



Scheme 1.5 – Mechanistic Differences Between 1,2-*Cis* and 1,2-*Trans* Donors

It is well established that the 1,2-stereochemical outcome of a glycosylation reaction is highly influenced by the nature of the protecting group used at the C2 hydroxyl of a glycosyl donor. Of the four possible 1,2-stereochemical arrangements in carbohydrates, two of them are often accessible using standard intermolecular reaction conditions. Selection of a C2 protecting group, which can actively participate in the resulting glycosylation, typically favors 1,2-*trans* glycosides (Scheme 1.6). This occurs because upon reacting with the anomeric center, the participating group blocks the *cis* face of the glycosyl donor. Incoming glycosyl acceptors are forced to approach the glycosyl donor from the opposite face. While 1,2-*trans* glycosides are typically accessed using this method, the strategy can still sometimes be unpredictable with poorly reacting glycosyl acceptors due to competing mechanisms.



Scheme 1.6 – Neighboring Group Participation to Give 1,2-*Trans* Glycosides

1.3) The Synthesis of 1,2-*Cis* Glycosides

The challenge of synthesizing *O*-glycosides with total stereoselectivity is one of the most difficult problems to solve in organic chemistry. While nature has evolved the ability to access the necessary glycosidic linkages through the evolution of enzymes[29], further progress is still needed for the development of chemical means to obtain the diverse array of glycosidic bonds possible. While a variety of glycosidic linkages can be obtained from natural sources, it is often difficult to purify individual glycosides. A vast number of chemical glycosylation strategies have been developed to help meet this challenge of obtaining glycosides in pure form. Despite the significant effort, the synthesis of 1,2-cis glycosides remains a daunting task and few general methods for the formation of these glycosides have been developed.[30]

Since poorly nucleophilic, hydroxylic glycosyl acceptors are typically used in glycosylation reactions, the majority of newly formed glycosidic bonds proceed through a unimolecular process. Since this mechanism proceeds through an sp^2-hybridized electrophilic carbon, the glycosyl acceptor may approach from either face to give the two

possible anomers. However, there are cases where a bimolecular mechanism has been shown to proceed.[31] While the orientation of the leaving group is typically irrelevant to the stereochemistry of the resulting glycoside, the bimolecular mechanism dictates that 1,2-trans donors provide 1,2-cis products and vice versa.

The stereochemistry of newly forming glycosidic bonds can be strongly influenced by the anomeric effect. Through hyperconjugative effects and the minimization of dipole-dipole interactions, the axial orientation is generally favored in the formation of new glycosides. The electronic nature of the effect is exhibited in the greater axial preference for more electronegative atoms forming the glycosidic bond. While the anomeric effect can provide easier access to α-glucosides, it also has a detrimental effect on the formation of β-mannosides.

Non-participating protecting groups are usually necessary at the C2 hydroxyl to obtain 1,2-cis glycosides. Particularly bulky C2 hydroxyl protecting groups have been shown to encourage attack at the opposite face of the oxocarbenium to give 1,2-cis glycosides. Furthermore, distal protecting groups can also have an effect on the stereochemistry of newly formed glycosidic bonds.[32] Protecting groups at the C6 hydroxyl have been shown to block the equatorial approach of glycosyl acceptors through participation with the anomeric center as well as through steric hindrance.

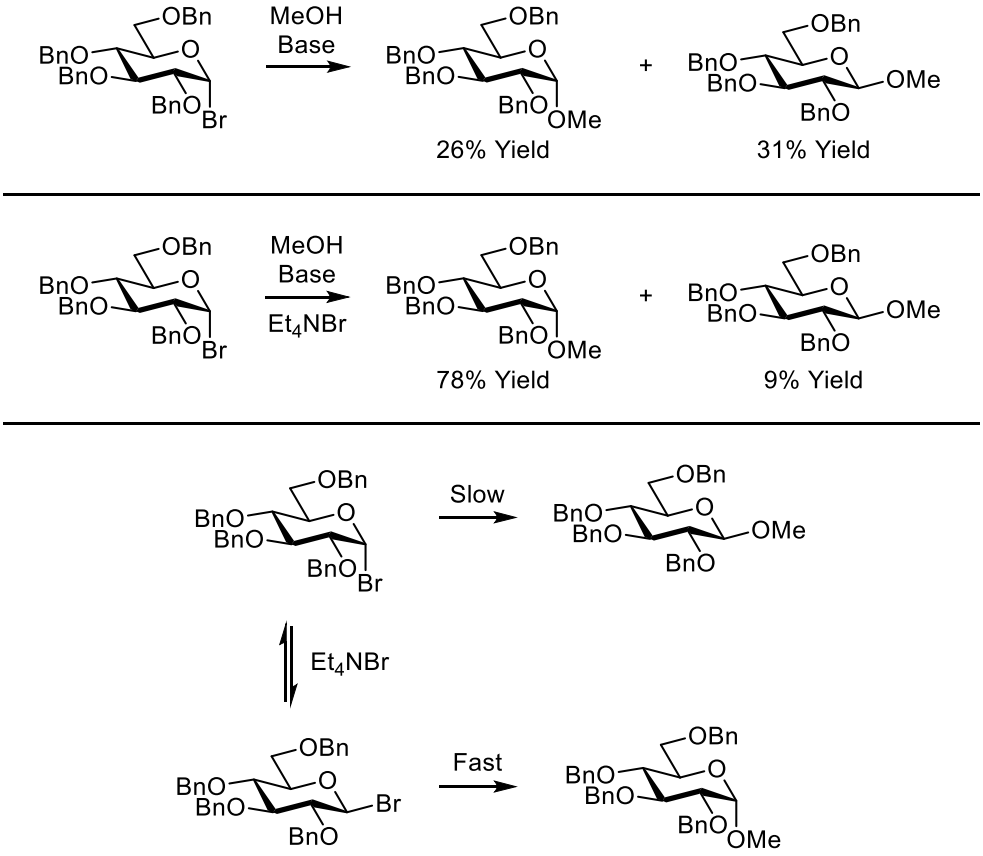
The polarity of a solvent used in a glycosylation has been shown to affect the stereochemistry of the resulting glycoside. Polar solvents can be used to encourage the formation of β-glycosides, most likely by reducing the charge separation often cited as the cause of the anomeric effect. Solvents can also interact and stabilize oxocarbenium

cations.[33,34] For example, acetonitrile adopts a temporary axial glycosidic bond with glycosyl donors and are displaced to give β-glycosides. Alternatively, ether-type solvents prefer an equatorial interaction with oxocarbeniums and favor the formation of α-glycosides.

The reactivity of the glycosyl acceptor also has an influence on glycosylation reactions. Unimolecular processes involving the nucleophilicity of alcohols tend to be less controllable due to faster reactivity. Therefore, primary alcohols can sometimes be difficult to use as glycosyl acceptors due to their high relative nucleophilicity.[35] Secondary alcohols, on the other hand, have been shown to exhibit better stereoselectivity in glycosylation reactions. The electronic nature of the glycosyl acceptor, due to its ability to influence the nucleophilicity of alcohols, can also impact the stereoselectivity. Electron withdrawing groups reduce the nucleophilicity of glycosyl acceptors and can help give stereocontrol to the reaction, while electron donating groups have the opposite effect.

One of the most influential attempts to synthesize 1,2-*cis* glycosides was reported by Lemieux in 1975.[36] Using the wealth of mechanistic knowledge about glycosylations accrued over the previous century, he found that adding Et_4NBr to reactions involving glycosyl bromides has a large impact on the resulting stereochemistry (Scheme 1.7). The reaction of a glucosyl bromide with methanol results in the formation of a roughly 1:1 anomeric mixture; however, the same reaction in the presence of Et_4NBr produces 78% of the α-glucoside with only 9% of the undesired β-glucoside. The stereoselectivity of the reaction is rationalized using the knowledge that β-glucosyl bromides react much more quickly than α-glucosyl bromides. The presence of Et_4NBr results in an *in situ*

anomerization of the glycosyl bromide donor. The more reactive β-anomer is coupled to methanol through a bimolecular displacement to provide the desired 1,2-cis glycoside. Since Lemieux's report, a variety of strategies using glycosyl halides have been developed for the synthesis of 1,2-cis glycosides; however, these donors can suffer from poor stability.[37]



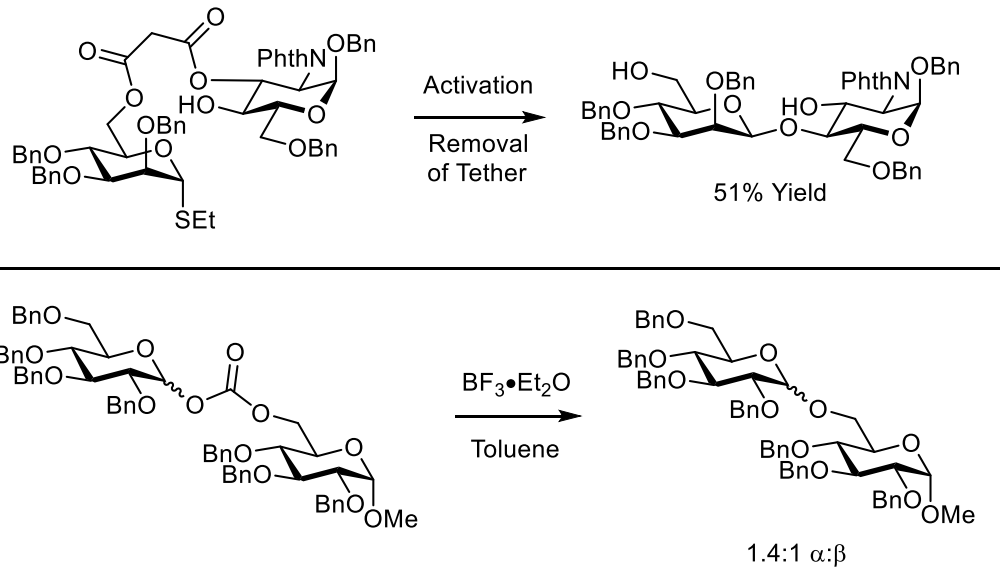
Scheme 1.7 – Lemieux's *in situ* Anomerization Strategy

A variety of other non-halide glycosyl donors have been used for the synthesis of 1,2-cis glycosides. Hemiacetals and a number of oxygen-derived glycosyl donors have been shown to provide these products depending on the reaction conditions.[30] Glycosyl phosphites have been activated using 2,6-di-*tert*-butylpyridinium iodide and Bu_4NI to give 1,2-*cis* glycosides, most likely through a Lemieux-like *in situ* anomerization to give

glycosyl iodides.[38] During the development of the iterative armed-disarmed glycosyl donor strategy, it was found that armed donors tend to provide greater amounts of 1,2-cis glycosides than disarmed donors.[30] Thioglycosides have also been used for the formation of 1,2-cis glycosides. Crich has reported a highly selective method to obtain β-mannosides using a 4,6-benzylidene acetal-protected thiosulfoxide donor. Activation using thiophenyl triflate results in an α-triflate which is displaced to give the product.[39]

As an alternative to chemical routes, a variety of enzymes have been used for the installation of 1,2-cis glycosidic bonds. In addition to β-mannosides and α-glucosides, α-galactosides[40] and α-fucosides[41] have also been obtained via enzymatic methods. Glycosyltransferases and glycosidases have both been used to form new 1,2-*cis* glycosides.[30]

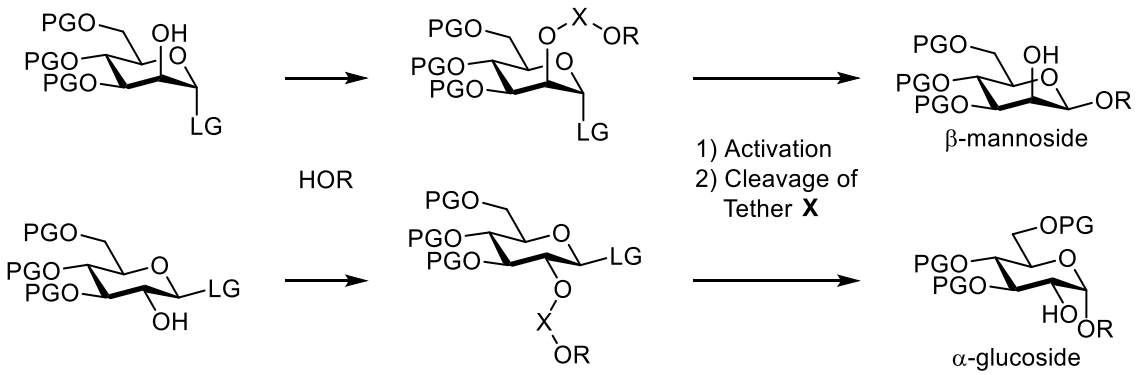
Indirect intramolecular processes have been developed to overcome the formation of 1,2-cis glycosides. Ziegler devised a strategy whereby a glycosyl acceptor is tethered to the C6 hydroxyl of a glycosyl donor through a malonate tether (Scheme 1.8).[42] Upon activation of the glycosyl donor, the unprotected C3 hydroxyl of the donor was delivered to the anomeric center. After cleavage of the malonate tether, the β-mannoside was obtained in 51% yield without any sign of the α-anomer. The structure of the tether can have a large impact on the reaction, as a succinate tether provides 45% of the α-anomer. A different approach is to attach the glycosyl acceptor to the leaving group of a glycosyl donor; however, the majority of work using this strategy has resulted in the 1,2-trans glycoside. A decarboxylative glycosylation strategy using BF_3•OEt_2 as the glycosylation promoter favored the formation of an α-glucoside with relatively poor stereoselectivity.[43]



Scheme 1.8 – Non-Direct Intramolecular Methods to Obtain 1,2-*Cis* Glycosides

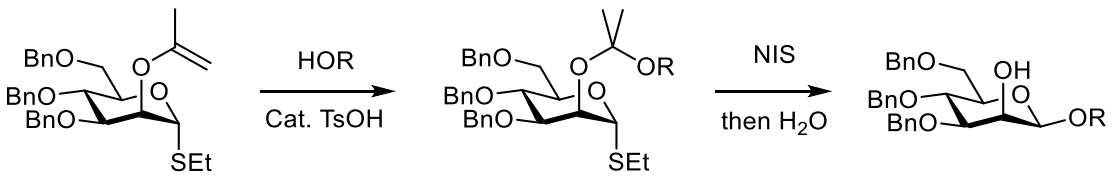
1.4) Direct Intramolecular Aglycone Delivery

One strategy to overcome the challenge of obtaining 1,2-*cis* glycosides is direct intramolecular aglycone delivery. In intramolecular aglycone delivery, or IAD, a glycosyl acceptor is first tethered to the C2 hydroxyl through a temporary linker (Scheme 1.9). Upon activation of the glycosyl donor, the now-tethered acceptor is forced to approach the anomeric center from the same face as the C2 hydroxyl. Once the new glycosidic bond is formed, the tethering atom can be removed to deliver either the β-mannoside or the α-glucoside. Using IAD, 1,2-*cis* glycosides are typically obtained with total stereocontrol.



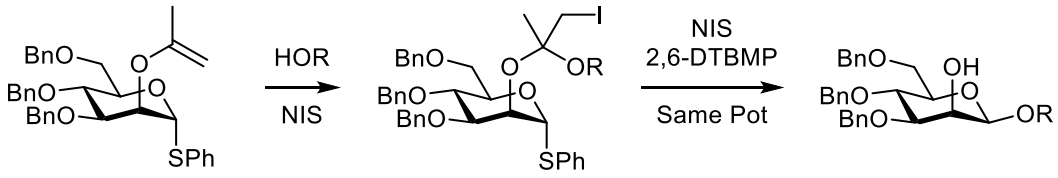
Scheme 1.9 – Intramolecular Aglycone Delivery to Give 1,2-*Cis* Glycosides

The concept of intramolecular aglycone delivery was first pioneered by Ole Hindsgaul as a strategy to obtain the synthetically difficult β-mannosides (Scheme 1.10).[44,45,46] Hindsgaul described a thiomannosyl donor protected by a vinyl ether at the C2 hydroxyl which is easily accessed by treating a C2-acetoxy-protected donor with the Tebbe reagent. In the presence of a hydroxylic glycosyl acceptor and catalytic tosylic acid, this donor could be converted to the mixed ketal. While primary alcohols were tethered efficiently, an increase in steric encumbrance resulted in lower yields due to scrambling of the mixed ketals to form symmetrical ketals. Activation of the glycosyl donor by NIS, followed by aqueous workup, gives β-mannosides with total stereoselectivity. Similar to the tethering step, the glycosylation step was very sensitive to steric bulk and the use of secondary alcohols was generally low yielding. Experiments were performed with exogenous methanol to deduce the mechanism of the reaction. Tethered primary acceptors were not affected by the exogenous alcohol; however, the more poorly reacting secondary acceptors experienced a reduction in yield and the formation of methyl β-mannoside. The stereoselective addition of methanol indicates that scrambling is taking place and that the reaction is most likely proceeding through an S_N2-like mechanism.



Scheme 1.10 – Hindsgaul's Mixed Acetal Strategy

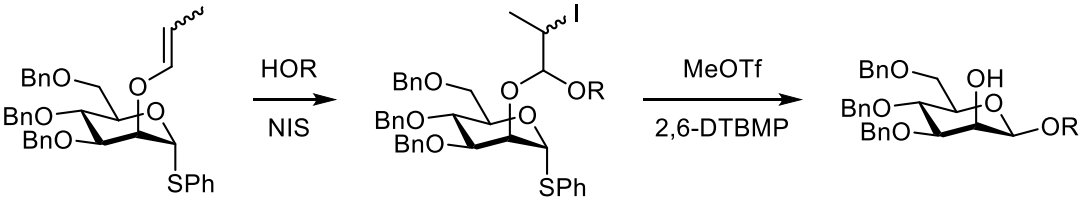
To overcome the challenge of ketal scrambling, Fairbanks explored an NIS-promoted tethering strategy (Scheme 1.11).[47,48] A variety of primary and secondary alcohols were shown to undergo the coupling efficiently; however, sterically bulky secondary alcohols were found to react sluggishly. The use of NIS as the tethering promoter also allowed the one pot tethering-glycosylation to give 1,2-cis glycosides. Both β-mannosides and α-glucosides could be obtained using this new strategy.



Scheme 1.11 – Use of NIS as Electrophile

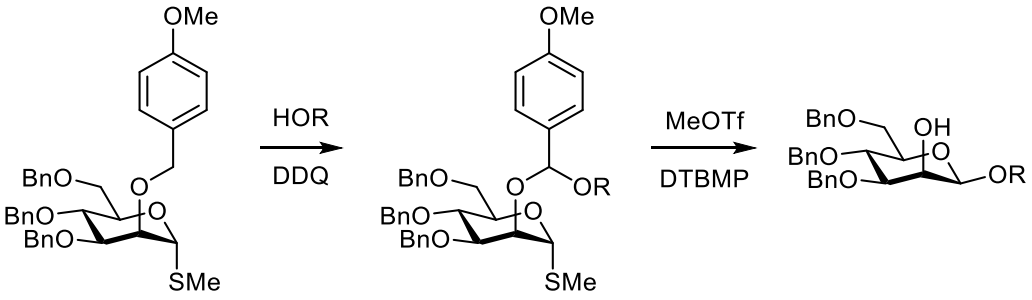
Fairbanks also studied the ability to use C2 enol ethers as tethers for intramolecular glycosylation (Scheme 1.12).[49,50] Enol ethers could be obtained efficiently from Wilkinson's catalyst and butyl lithium. The use of NIS to promote the tethering of these enol ethers with alcohols was typically high yielding, but the tethering of bulky alcohols was again sluggish and competition with succimide resulted in lower yields. A variety of iodonium electrophiles were explored and it was found that IDCT generated *in situ* from I_2, collidine, and AgOTf worked best for the tethering of hindered secondary alcohols. Thioglycosides and glycosyl fluorides were both suitable for the synthesis of β-

mannosides and α-glucosides. Later on, the method was applied to cyclic five-membered carbohydrates to obtain α-glucofuranosides with total stereoselectivity.



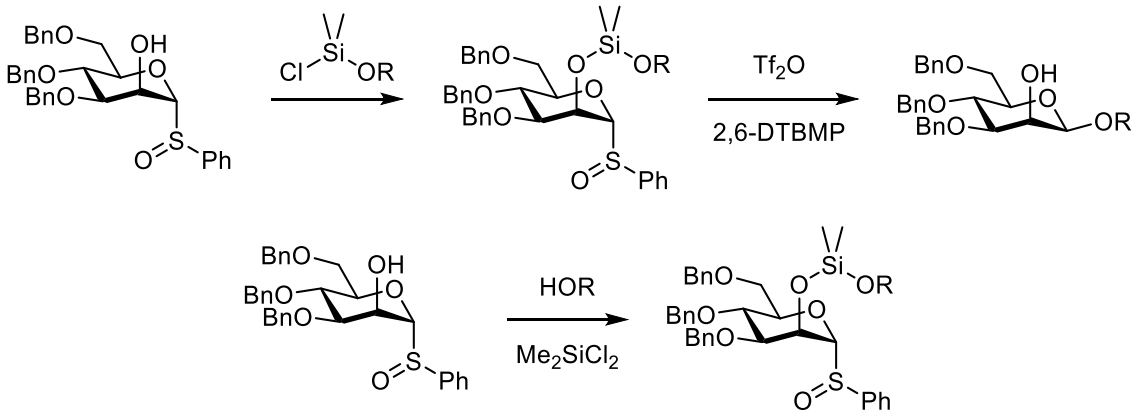
Scheme 1.12 – Enol Ethers as Tethers

Ito has studied the oxidative coupling of alcohols and glycosyl donors protected with PMB ethers at the C2 hydroxyl (Scheme 1.13).[51,52] The PMB ether can be oxidized using DDQ in the presence of an alcohol to form mixed acetals. Subsequent activation of the methyl thioglycoside donor with MeOTf resulted in efficient intramolecular delivery to yield the corresponding β-mannosides. While the intramolecular delivery of secondary glycosyl acceptors is often inefficient, the use of Ito's method enables the formation of a variety of disaccharides with total stereoselectivity. Cyclic rigidifying protecting groups such as cyclohexylidenes and cyclic silyl ethers were shown to increase yields by encouraging S_N2-type glycosylations.[53] The strategy has also proven to be useful in obtaining β-mannofuranosides.



Scheme 1.13 – PMB Ethers as Tethers

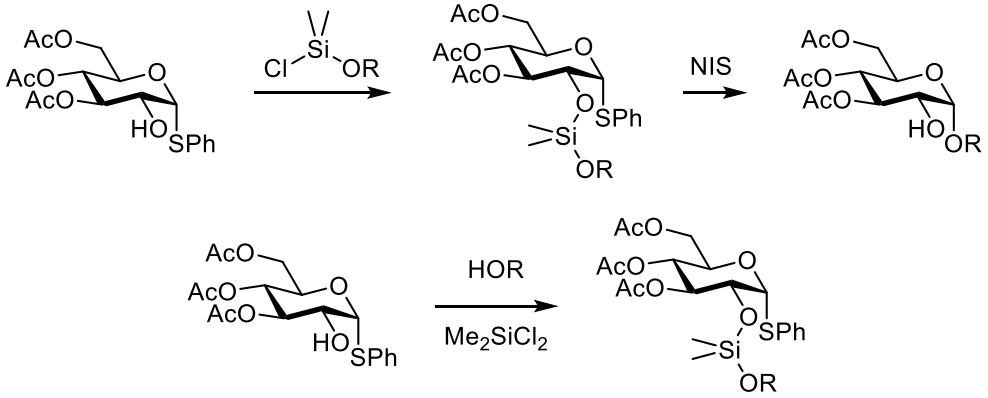
In addition to carbon, silicon has been explored as the tethering atom for intramolecular aglycone delivery. Stork first treated a hydroxylic glycosyl acceptor with dichlorodimethylsilane to provide an electrophilic aglycone (Scheme 1.14).[54] The treatment of a mannosyl sulfoxide with this prefunctionalized glycosyl acceptor provided the tethered intermediate in near quantitative yield. Activation of the sulfoxide functionality resulted in stereospecific transfer of the aglycone to give the β-mannoside. The orientation of the anomeric leaving group was shown to have no effect on the glycosylation. A later report detailed that glycosyl donors and glycosyl acceptors can be stirred together with dichlorodimethylsilane to avoid the necessity of aglycone prefunctionalization.[55] The method was shown to work with a variety of carbohydrate glycosyl acceptors; however, the C4 hydroxyl was not glycosylated efficiently due to deprotection and competition of the C6 hydroxyl.



Scheme 1.14 – Silicon Tethers to Obtain β-Mannosides

While Stork was developing methodology to obtain β-mannosides, Bols was concurrently using a similar strategy for the synthesis of α-glucosides (Scheme 1.15).[56,57,58] Bols also used a prefunctionalized glycosyl acceptor to form tethered intermediates, but he instead used thioglycosides as the glycosyl donors. Primary,

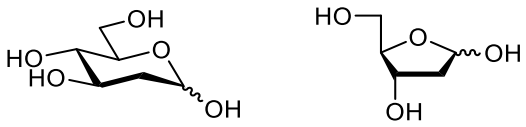
secondary, and tertiary alcohols all underwent the coupling efficiently. Tethered intermediates were activated in the presence of NIS to afford the α-mannosides. Unlike some previous examples of intramolecular aglycone delivery, sterically encumbered glycosyl acceptors were able to undergo the process in good yield. The scope of the glycosyl donor was later expanded to include α-galactosides.



Scheme 1.15 – Silicon Tethers to Obtain α-Glucosides

1.5) Synthesis of 2-Deoxy-β-Glycosides

A wide variety of deoxysaccharides have been found to have active roles in biologically active compounds. Over a hundred naturally occurring deoxysaccharides have been isolated (Scheme 1.16).[59] In particular, 2-deoxy carbohydrates have been found widely distributed in natural products.[60,61] Furthermore, the backbone of DNA is made up of repeating 2-deoxy-ribose units. As the biological significance of 2-deoxy carbohydrates has become better elucidated, interest in chemotherapeutics incorporating these structures has increased.

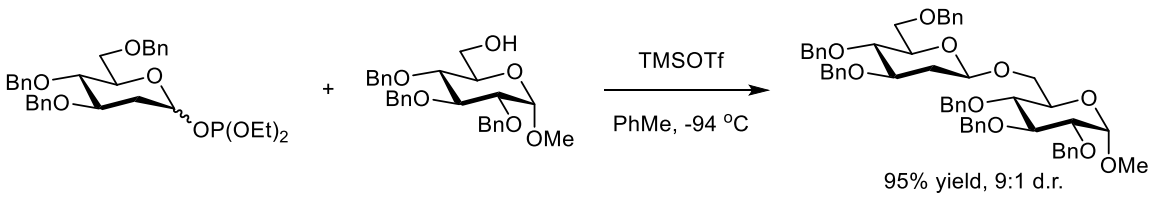


Scheme 1.16 – 2-Deoxy-Glucose and 2-Deoxy-Ribose

Increased interest in 2-deoxy carbohydrates and glycoconjugates bearing these sugars has driven the desire for access to these carbohydrates through chemical methods. However, the synthesis of 2-deoxy carbohydrates can be a particularly difficult task. The lack of a directing group at the C2 position can make controlling the stereochemistry of a newly formed glycosidic bond very difficult. Furthermore, the anomeric effect has been shown to encourage the formation of 2-deoxy-α-glycosides.

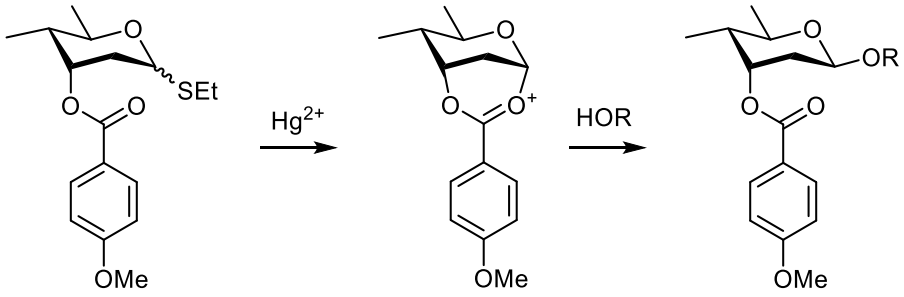
A variety of strategies has been developed to overcome the challenge of 2-deoxy-β-glycoside synthesis. The inherent nature of installing β-glycosidic functionality in 2-deoxy carbohydrates has made the development of general methods difficult. A number of variables have been shown to influence the stereochemistry of newly formed 2-deoxy glycosides. These variables include the temperature, protecting group scheme, solvent, anomeric leaving group, and glycosylation promoter.[62]

The vast majority of leaving groups have been shown to favor the formation of 2-deoxy-α-glycosides.[63] Alternatively, 2-deoxy glycosyl phosphites have been shown to favor the formation of 2-deoxy β-glycosides. Hashimoto reported that the activation of these donors with TMSOTf provided 2-deoxy-β-glycosides in very high yield and with diastereoselectivity as high as 9:1 (Scheme 1.17).[64] The source of diastereoselectivity is presumed to be an α-triflate intermediate which can then be displaced to give the desired glycoside.



Scheme 1.17 – Glycosyl Phosphites as Glycosyl Donors

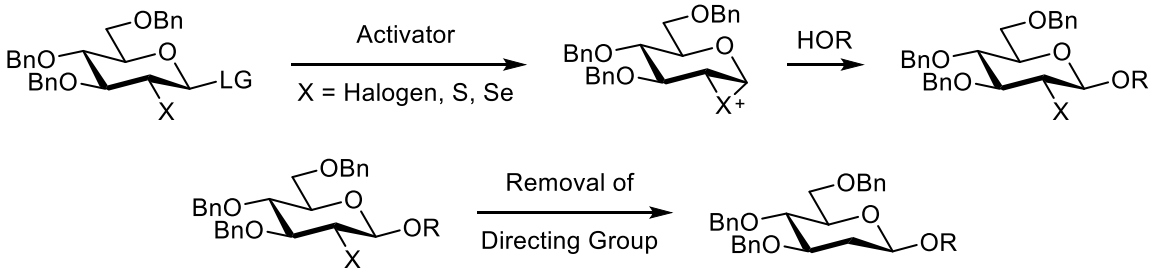
The synthesis of β-glucosides is often accomplished by using a protecting group at the C2 hydroxyl that can participate with the anomeric oxocarbenium ion. The lack of a hydroxyl in 2-deoxy glycosides limits the use of this strategy; however, more distal protecting groups can still influence new glycosidic bonds. During his synthesis of digitoxin, Wiesner utilized a participating protecting group at the C3 hydroxyl (Scheme 1.18).[65] While limited to donors with axial substituents at the C3 position, a para-methoxy substituted benzoyl protecting group was able to donate into the oxocarbenium ion and block the bottom face. Displacement by the incoming glycosyl acceptor resulted in the synthesis of 2-deoxy-β-glycosides.



Scheme 1.18 – Anchimeric Assistance from C3 Hydroxyl

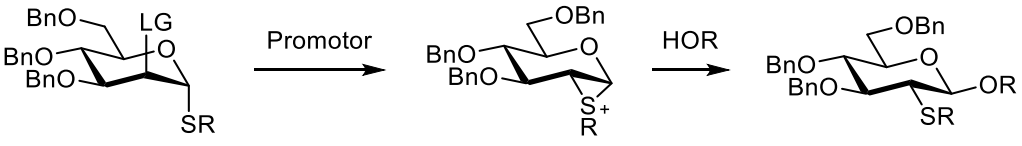
Another strategy to synthesize 2-deoxy-β-glycosides is the use of temporary directing groups. A variety of equatorial halogen, sulfur, and selenium glycosyl donors are suitable for the installation of new β-glycosidic bonds.[66] A participating-type mechanism is thought to account for the stereoselectivity of the reaction (Scheme 1.19).

This strategy requires the stereoselective installation of a C2 directing group, which can sometimes be difficult itself. Activation of the glycosyl donor results in oxocarbenium participation by the C2 directing group. Alternatively, glycals have been used to undergo both the installation of the directing group and the formation of a new glycosidic bond in one step. In both cases, the removal of the directing group is necessary to obtain the 2-deoxy-β-glycoside.



Scheme 1.19 – Use of Temporary Directing Groups

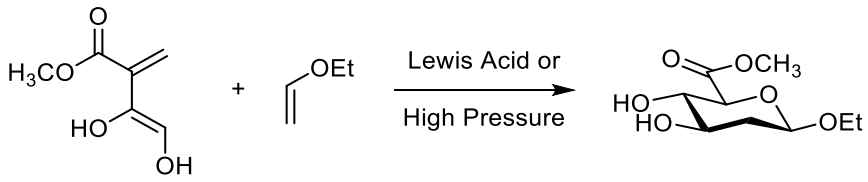
A similar strategy involves the stereocontrolled installation of a leaving group at the C2 position (Scheme 1.20). To obtain β-glycosides, the leaving group must be in axial orientation. Additionally, this thioglycoside must be in a 1,2-trans configuration. Upon activation, the sulfur undergoes a nucleophilic attack to form a sulfonium ion which can block the bottom face of the glycosyl donor. Incoming nucleophiles displace the sulfonium at the anomeric position to give β-glycosides; however, it is still necessary to remove the sulfur from the C2 position following the 1,2-migration.



Scheme 1.20 – 1,2-Migration of Thioglycosides

2-Deoxy glycosides can also be accessed using glycosyl donors functionalized with oxygen or nitrogen at the C2 position. The use of participating protecting groups can provide 1,2-trans glycosides in very high yield. A radical deoxygenation of the C2 hydroxyl can be high yielding; however, the reduction often requires organotin reagents and the strategy can be susceptible to radical byproducts. Alternatively, the conversion of a C2 hydroxyl to a C2 triflate is typically high yielding and the triflate can be reduced using Bu_4NBH_4.[67,68] Glucosamines are also able to undergo deoxygenative processes at the C2 position and can be used to obtain 2-deoxy-β-glycosides.[69]

Finally, a creative alternative to access 2-deoxy-β-glycosides is the use of pericyclic reactions. Pericyclic reactions are especially attractive for the synthesis of glycosides due to their selective formation of new stereocenters. Boger and Robarge were able to react highly functionalized dienes with enol ether dienophiles to give functionalized carbohydrates through cycloaddition reactions. (Scheme 1.21).[70,71] The reactions were very stereoselective and reduction of the requisite ester functionality provides 2-deoxy-β-glycosides.



Scheme 1.21 – Cycloaddition to form 2-deoxy-β-Glycoside

Chapter 2

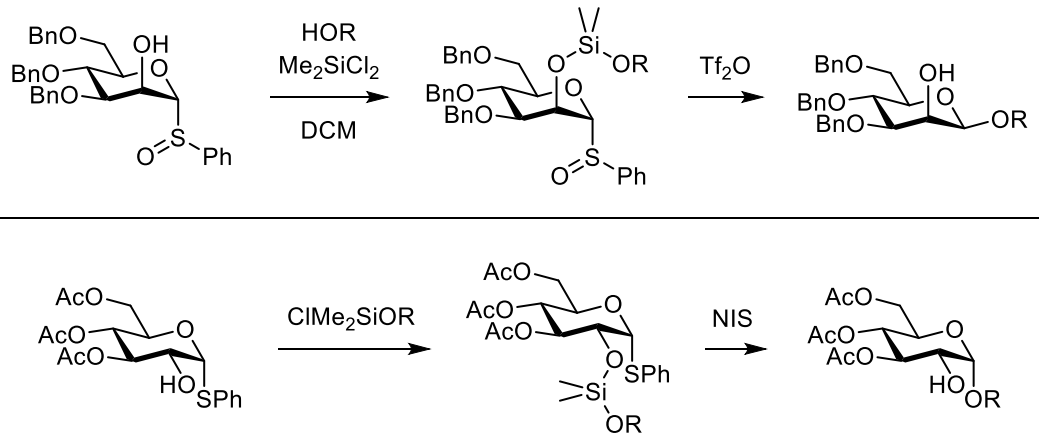
Review of Sugar Silanes

2.1) Introduction

Due to the important effects of a glycan's structure on the resulting glycoconjugate's biological function, the chemical synthesis of glycosides continues to be an important target of research. However, the inherent properties of oligosaccharides give them immense complexity and their chemical syntheses require a detailed strategy for controlling both regio- and stereoselectivity. Despite the enormous progress that has been made in the development of chemical glycosylation methods, challenges remain in the efficiency and stereoselectivity of carbohydrate installation. Access to the various 1,2-stereochemical arrangements from a common carbohydrate donor is challenging, as careful matching of the anomeric leaving group, protecting groups that influence stereochemistry and reactivity, and reaction conditions is often required. The vast majority of methods require that only a single hydroxyl group is unmasked in the acceptor substrate. Furthermore, utilization of acceptor substrates other than alcohols and reactive electrophiles are virtually unexplored.[72,73,74]

While 1,2-*trans* glycosides can often be afforded using C2 neighboring group participation, it can be quite challenging to obtain 1,2-*cis* glycosides selectively. One strategy to overcome these limitations has been the use of intramolecular aglycone

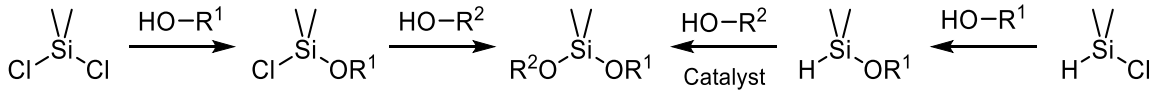
delivery, whereby an aglycone is first tethered to the glycosyl donor and then delivered to the anomeric center stereospecifically. Stork and Bols have shown that dimethylsilylketals are particularly good tethers for the synthesis of both β-mannosides and α-glucosides (Scheme 2.1).[54,55,56,57,58] Access to the necessary donor-acceptor tethered materials requires the handling of sensitive chlorodimethylsilyl ether intermediates. Improved routes to the requisite tethered substrates and expansion of the range of accessible classes of glycoside products would broaden the appeal and utility of these methods.



Scheme 2.1 – Dimethylsilylketals Tethers for Intramolecular Aglycone Delivery

Although bis-electrophilic reagents are commonly used in the assembly of silyl linkages between two hydroxyls, the possibility for homocoupled byproducts decreases the efficiency with which the tethered intermediates may be made (Scheme 2.2). Alternatively, Me_2SiHCl enjoys the advantage of high heterocoupling across a range of substrates due to the reactivity differences between silicon-chloride and silicon-hydride bonds.[75,76] Considering the Montgomery group's experience with organometallic

transformations, this expertise could be used to improve the tethering process for intramolecular aglycone delivery.



Scheme 2.2 – Chlorosilanes for Efficient Heterocoupling

To address the above challenges and limitations, our group has focused on the development of "sugar silanes," or carbohydrate-bearing silane reducing agents. Sugar silanes provide a silicon-hydride functional handle with which a variety of potential catalysts and glycosyl acceptors may react. The goal of the sugar silane project was to develop sugar silanes as a versatile reagent class to enable an array of glycosylation processes, providing access to numerous 1,2-steroechemical relationships and utilizing several different types of donor substrates (Figure 2.1).

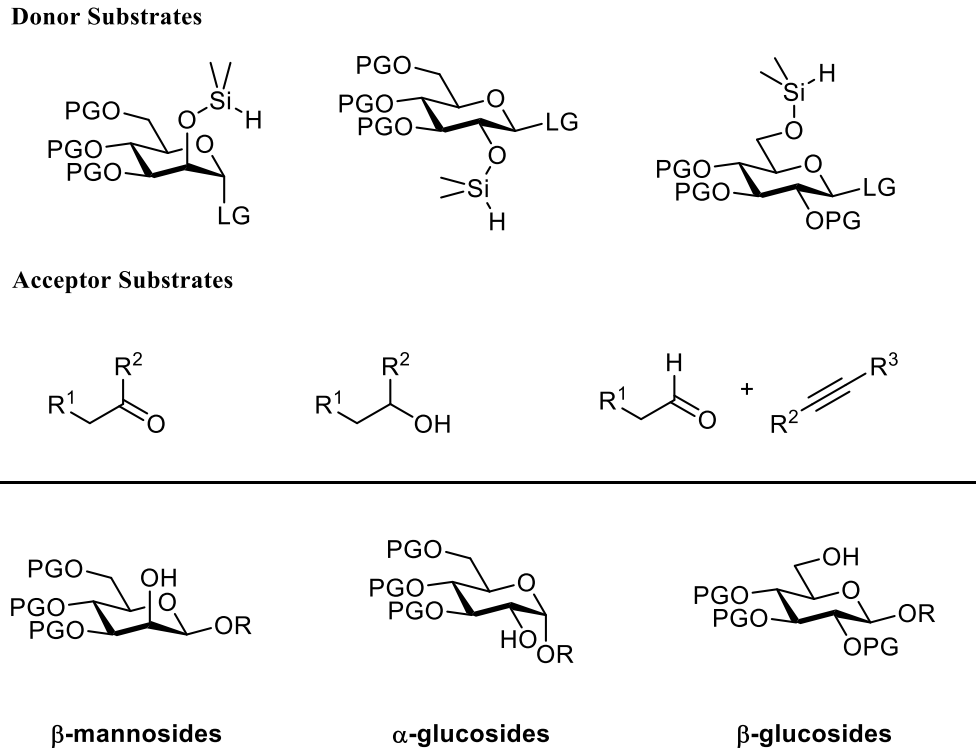
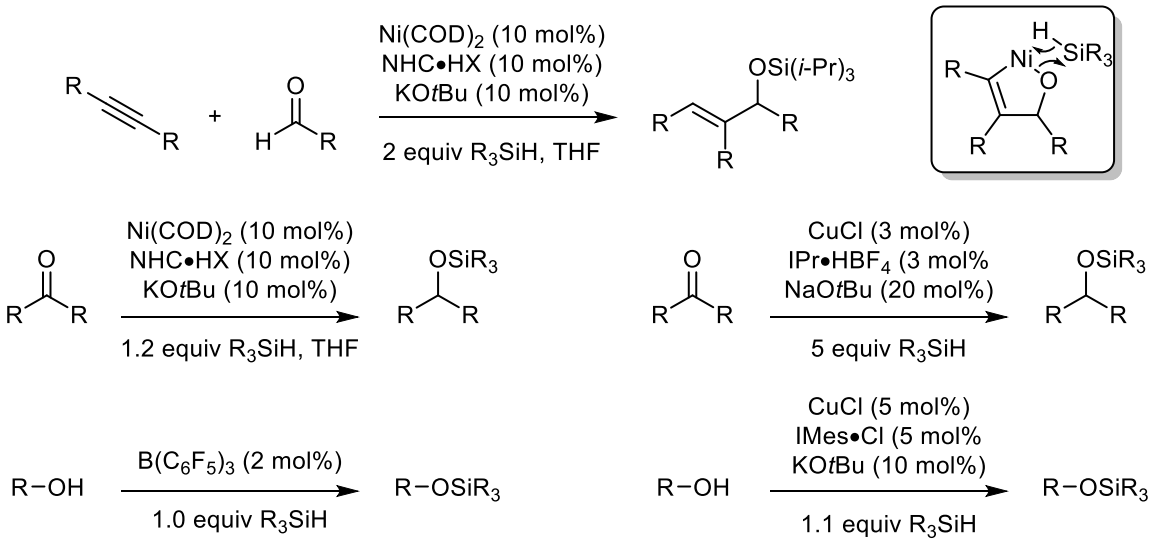


Figure 2.1 – The Versatility of Sugar Silanes

The majority of chemical glycosylations are derivative of the Koenigs-Knorr method where a glycosyl donor has a leaving group installed at the anomeric position.[77] Activation of the leaving group gives an oxocarbenium cation which can then be trapped by an alcohol to give the resulting glycoside. Our group has envisioned using our expertise in the field of organometallic catalysis to access glycosyl acceptors in non-traditional ways. A variety of transition metal and Lewis acid catalysts have been shown to promote the formation of oxygen-silicon bonds. These reactions include the coupling of aldehydes and alkynes to give silyl ether protected allylic alcohols[78] as well as the hydrosilylation of ketones[79,80,81] and the dehydrogenative silylation of alcohols[82,83] (Scheme 2.3). Since the use of silicon as a tether in intramolecular aglycone delivery requires the formation of a silicon-oxygen bond, alternative routes which do not require

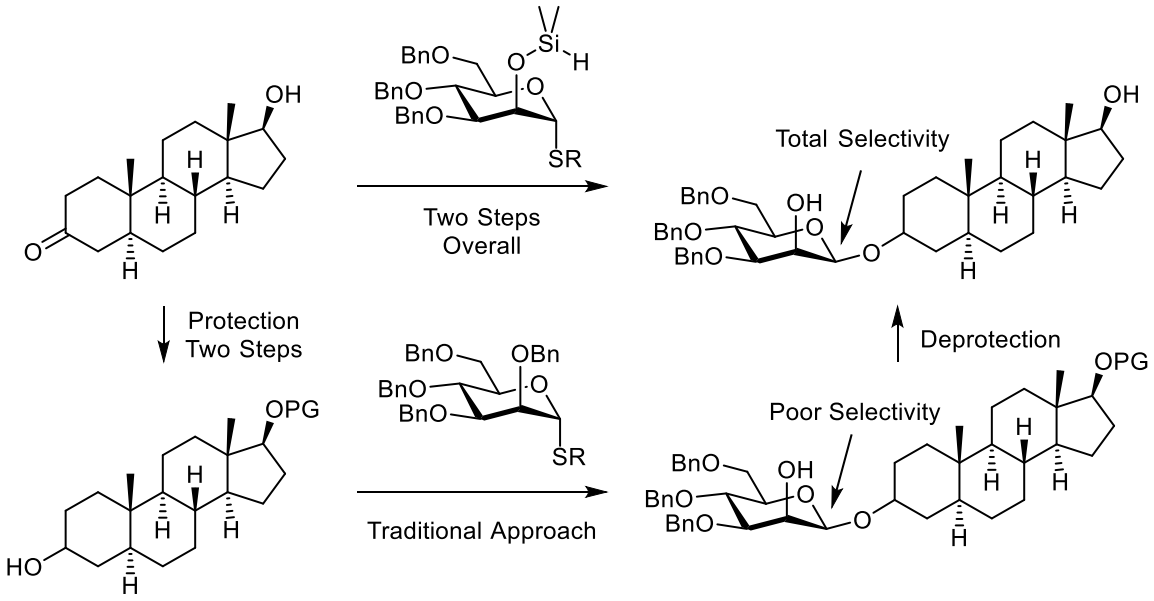
the nucleophilicity of an alcohol represent a new orthogonal route from which silyl intermediates may be targeted.



Scheme 2.3 – Transition Metal Catalyzed Formation of Oxygen-Silicon Bonds

The ability to chemoselectively form a glycosidic bond at an electrophilic position of an aglycone is a different approach. The transition-metal catalyzed hydrosilylation of a carbonyl provides unique reactivity within the scope of intramolecular aglycone delivery. While previous methods have depended on the isolated nucleophilicity of a hydroxyl group, the silicon-hydride functionality allows new nucleophile-tolerant processes which target previously unreactive functional groups. The chemoselectivity of organometallic catalysts could provide more efficient routes to glycosylated compounds. For example, a sugar silane could be reacted with a hydroxyketone to provide hydrosilylated intermediates (Scheme 2.4). Subsequent glycosylation would provide the glycoside in only two steps. A more traditional route to this glycoside would require first masking the hydroxyl group through protecting group chemistry followed by reduction of the ketone. Glycosylation could then proceed using the nucleophilicity of the newly created alcohol;

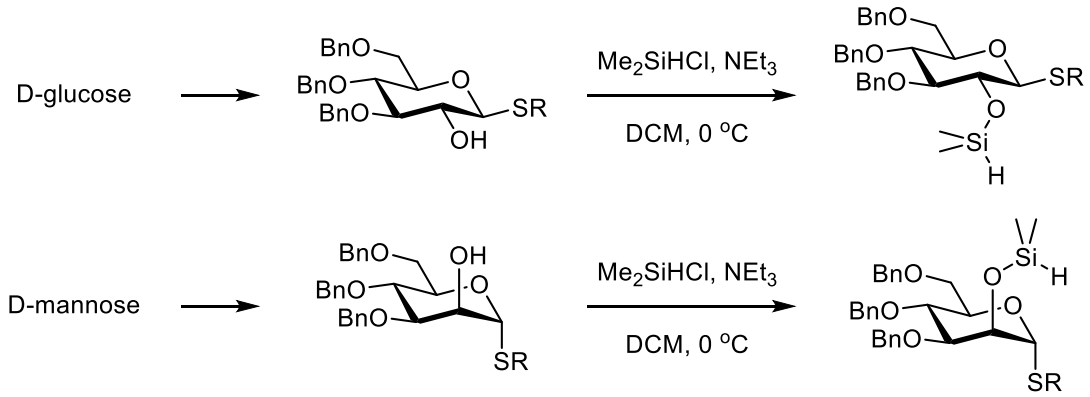
however, the formation of 1,2-*cis* glycosides is notoriously difficult and often provides poor diastereoselectivity. After the glycosylation, it would still be necessary to remove the protecting group that was installed earlier in the synthesis. While a traditional approach to this glycoside would require a minimum of four steps, inefficient protecting group transformations, and poor glycosylation stereoselectivity, sugar silanes offer an efficient alternative strategy to overcome these limitations.



Scheme 2.4 – Sugar Silane Approach Versus Traditional Approach

The synthesis of sugar silanes follows well-known routes to obtain common thioglycoside donors (Scheme 2.5). Beginning with the respective glucose or mannose monosaccharide, high yielding functional group manipulations are performed that require relatively minimal purification. The synthesis is easily performed on a multi-gram scale and only one chromatographic separation is necessary to obtain the desired sugar silane. Upon obtaining pure phenyl 3,4,6-*O*-tribenzyl-thioglucoside or -mannoside, the compound is treated with dimethylchlorosilane and triethylamine to afford the pure sugar

silane upon aqueous workup. Chromatography of the sugar silane is unnecessary as the byproducts are volatile. While unsuitable for long-term storage on the bench top due to hydrolysis of the dimethylsilane, sugar silanes are stable under vacuum or can be stored as a frozen solution in benzene indefinitely. Alternatively, the precursor thioglycoside is stable and can be efficiently transformed to the sugar silane as needed.

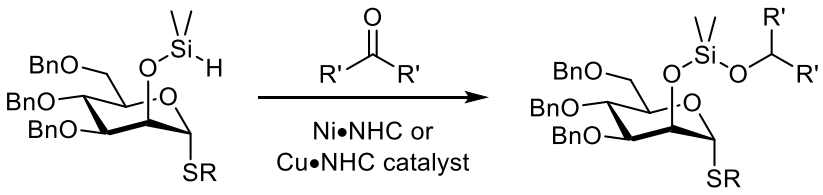


Scheme 2.5 – Synthesis of C2 Functionalized Sugar Silanes

2.2) Hydrosilylation of Ketones

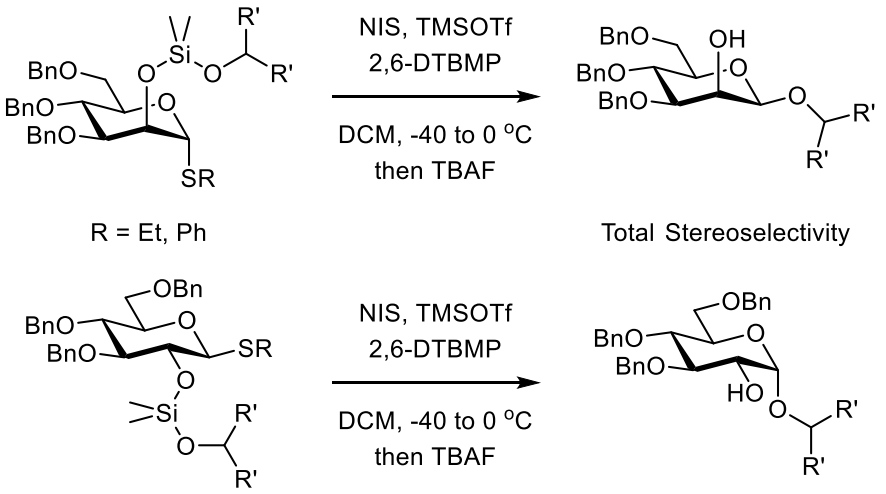
A benefit of using sugar silanes includes the vast library of organometallic transformations involving a silicon hydride bond. Where the displacement of a silyl chloride might suffer from difficulties inherent to nucleophilic substitution reactions, the variety of transition metal catalysts and reaction conditions available to interact with silicon hydride bonds lends tunability to the reaction. With expertise in the field of nickel-catalyzed transformations, former group member Dr. Zack Buchan chose a nickel-NHC catalyst to examine the hydrosilylation of ketones using sugar silanes (Scheme 2.6). Gratifyingly, near quantitative yields were obtained using unhindered ketones with this catalyst. Unfortunately, a decrease in yield occurred when more hindered ketones were used. A copper-NHC catalyst developed by Nolan has been shown to improve the ability

to hydrosilylate hindered ketones.[80] Attempts to hydrosilylate hindered ketones with sugar silanes using this catalyst proceeded efficiently, providing a toolbox whereby a suitable catalyst could be chosen based on the nature of the ketone.



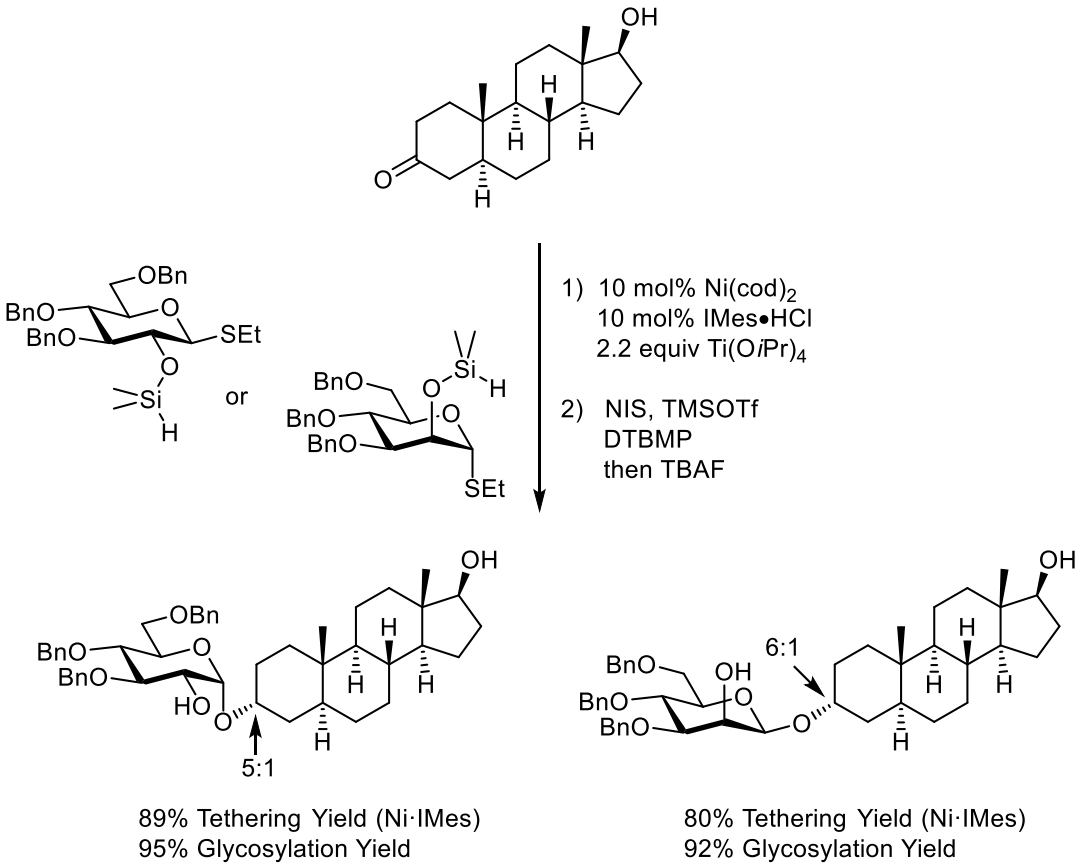
Scheme 2.6 – Hydrosilylation of Ketones Using Sugar Silanes

After the hydrosilylation of ketones with sugar silanes, the resulting tethered intermediates were activated using NIS, TMSOTf, and DTBMP (Scheme 2.7). The glycosyl donor is activated at -40 °C and the reaction is warmed to 0 °C to ensure complete reactivity. Both ethyl and phenyl thioglycosides are suitable for the procedure; however, more hindered glycosyl acceptors are higher yielding with the more reactive thiophenyl leaving group. A number of unhindered and hindered ketones were used to obtain a variety of α-glucosides and β-mannosides. Furthermore, amines and ketals were shown to tolerate the coupling and subsequent glycosylation.



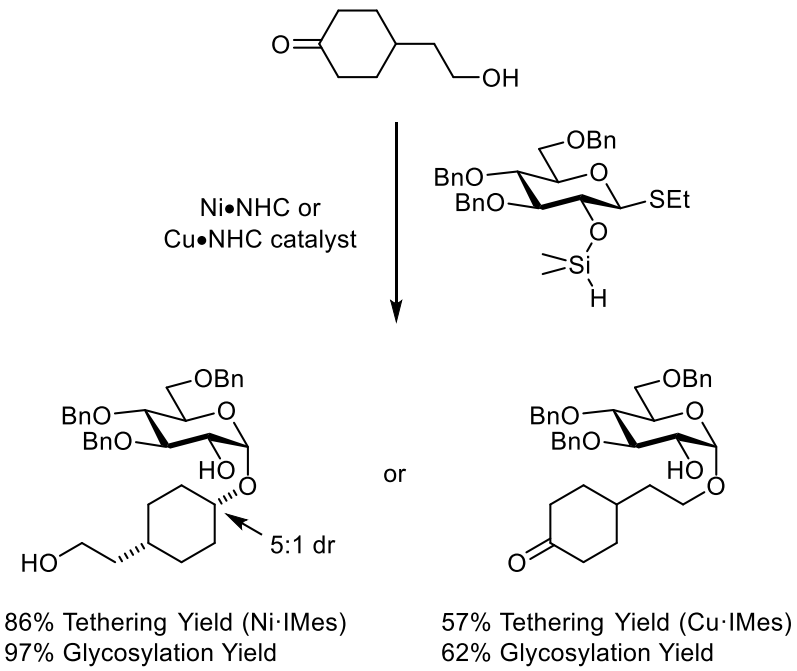
Scheme 2.7 – Glycosylation of C2 Sugar Silanes

The majority of glycosylation reactions utilize the nucleophilic reactivity of hydroxyl groups to form the new glycosidic bond. Complex glycosyl acceptors with multiple nucleophilic groups can require extensive, wasteful protecting group manipulations to attain the desired reactivity. As ketones are unusual coupling partners for glycosylation reactions, one of the exciting implications of chemoselective catalysis using sugar silanes is the ability to avoid protecting group chemistry and use the catalyst to dictate where the new glycosidic bond is formed. As a proof of principle, the chemoselective hydrosilylation of dihydrotestosterone was performed using the nickel-IMes catalyst (Scheme 2.8). The subsequent glycosylation was high yielding and both β-mannosides and α-glucosides could be obtained with total diastereoselectivity depending on the sugar silane used.



Scheme 2.8 – Site Selectivity with Sugar Silanes

The choice of organometallic catalyst also provides an opportunity for chemoselectivity. A simple hydroxy ketone was treated with sugar silane and nickel-IMes to provide the hydrosilylated product. Alternatively, copper-IMes could be used to favor the dehydrogenative silylation product. Glycosylation of the tethered intermediates provided α-glucosides based off of which catalyst was used. This catalyst-controlled reversal of chemoselectivity in hydroxyketone functionalization with silanes is unprecedented and offers a powerful new tool for the formation of new glycosidic bonds (Scheme 2.9).



86% Tethering Yield (Ni·IMes)
97% Glycosylation Yield

57% Tethering Yield (Cu·IMes)
62% Glycosylation Yield

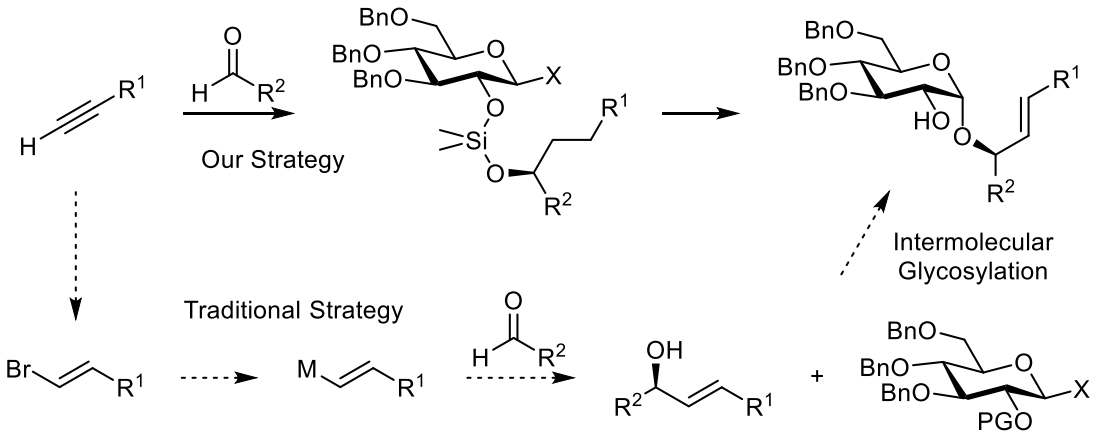
Scheme 2.9 – Chemoselectivity Using Sugar Silanes

The use of sugar silanes allows for the conversion of ketones into new glycosidic bonds without the need to utilize the reactivity of a hydroxyl group. Furthermore, the ability to chemoselectively obtain the glycoside resulting from the selective hydrosilylation of ketones or the dehydrogenative silylation of alcohols provides a more efficient route to these products and eliminates wasteful protecting group steps. These tools highlight initial steps to show the power of merging organometallic catalysis with glycosylation chemistry.

2.3) Aldehyde and Alkyne Coupling

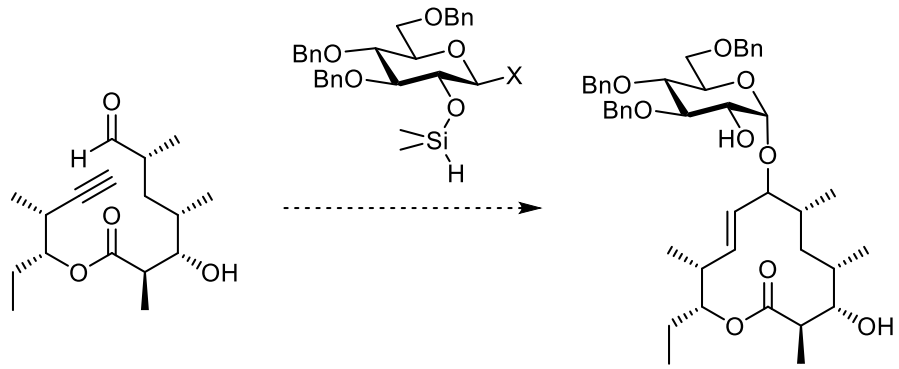
Another weakness of traditional glycosylation strategies is the necessity of linear synthetic pathways towards the synthesis of aglycones. These linear pathways are rarely atom economical and significant time must be spent on protecting group chemistry. Since the synthesis of a single aglycone can require considerable resources, it can be a time-

consuming process to synthesize a variety of glycosylated aglycones. A more efficient approach would incorporate the aglycone synthesis itself into the glycosylation process (Scheme 2.10). Silyl hydrides have been utilized as reducing agents in a variety of chemical processes. Since the nickel-catalyzed reductive coupling of alkynes and aldehydes results in the formation of allylic silyl ethers, this process could be modified to use sugar silanes as the reducing agent. This would incorporate a glycosyl donor into the carbon-carbon bond forming process and provide an efficient route to 1,2-*cis* glycosides following the synthesis of the aglycone.



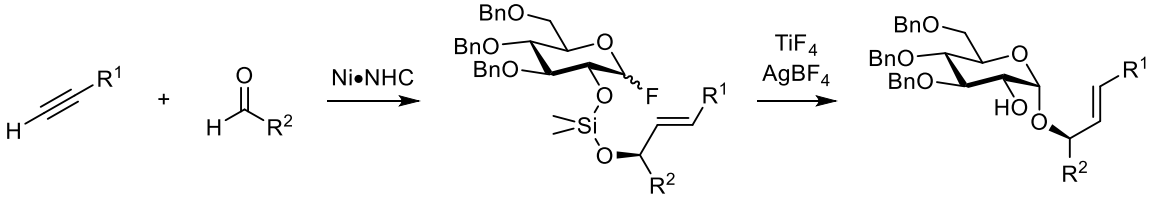
Scheme 2.10 – Sugar Silane Approach Versus Traditional Approach

This strategy can be used to complete the synthesis of complex aglycones while also serving as a route to challenging glycosidic bonds. For example, the synthesis of a macrolactone could be finished through an intramolecular aldehyde-alkyne coupling (Scheme 2.11). The resulting sugar silane functionalized allylic alcohol could then undergo an intramolecular glycosylation to provide the glycosylated product in only two steps.



Scheme 2.11 – Efficient Route to Glycosylated Macrocycle

Former group member Dr. Katie Partridge showed that the diastereoselectivity of the aldehyde-alkyne coupling with sugar silanes using nickel-IMes as the catalyst results in poor diastereoselectivity for the newly formed hydroxylic chiral center. This result was expected, as the silyl-hydride reducing agent is not involved in the carbon-carbon bond-forming step. A chiral NHC was found to improve the diastereoselectivity of the reaction to as high as 5.7:1 and both diastereomers could be synthesized depending on which enantiomer of ligand was used. Thioglycosides were found to be unsuitable due to decomposition during the glycosylation, but glycosyl fluorides provided the glycosylated products in good yield (Scheme 2.12). A variety of aldehydes and alkynes were successfully used and the method tolerated ketones, esters, and alcohols. Additionally, a sterically bulky ligand was shown to fully reverse the regioselectivity of the reaction and provide branched products.



Scheme 2.12 – Aldehyde-Alkyne Coupling to Access Glycosylated Alcohols

The incorporation of sugar silanes into aldehyde-alkyne couplings expands the versatility with which these reagents may be used. Regio- and diastereocontrol is offered through the ligand-controlled formation of a new carbon-carbon bond to provide tethered intermediates, which can be subsequently reacted to provide challenging glycosidic bonds. This strategy also allows for the completion of aglycone syntheses in a combined effort towards synthesizing glycosides.

2.4) Dehydrogenative Silylation of Alcohols

Prior efforts by former group members Dr. Zack Buchan and Dr. Katie Partridge have demonstrated the success of sugar silanes in the direct reductive glycosylation of carbonyl substrates and the three-component assembly of glycosylated products via the catalytic union of aldehydes and alkynes. In order to provide a more complete toolbox of glycosylation procedures from sugar silanes, it is important to provide an efficient route to access hydroxylic glycosyl acceptors through dehydrogenative silylations. While the previous work by Stork and Bols utilized alcohols, the efficiency of the process suffers from the use of bis-electrophilic dichlorodimethylsilane. In addition to extra halide waste, bis-electrophilic reagents suffer from the formation of homodimer products. The use of chlorodimethylsilane enjoys the advantage of high heterocoupling efficiency across a range of alcohol substrates. Following chloride displacement to form sugar silanes, a second alcohol can condense with the resulting silyl hydride (losing H_2) in the presence of a transition metal or Lewis acid catalyst, thus effectively preventing homocoupling across a range of substrate combinations.

Upon screening numerous catalyst systems to promote the dehydrogenative coupling with alcohol acceptors, Dr. Zack Buchan identified two catalyst systems as most robust and exhibiting complementary behavior. While the methods were often interchangeable with similar results, the use of $B(C_6F_5)_3$ was most effective with more hindered 2° and 3° alcohol substrates,[82] whereas a copper-IMes catalyst was most effective with 1° alcohols (Table 2.1).[83] Couplings of menthol with glucose sugar silane are effective using either CuCl-IMes or $B(C_6F_5)_3$ as catalyst, with the latter promoting dehydrogenative coupling to afford the tethered intermediate in near quantitative yield. Intramolecular glycosylation with NIS, TMSOTf, and DTBMP cleanly afforded α-glucoside **1** as a single diastereomer in 98% isolated yield. Alternatively, mannose sugar silane allowed the production of β-mannoside **2** in excellent overall yield as a single stereoisomer. The versatility of the method was shown in the use of a sugar silane containing both acetal and silyl ether protecting groups. Interestingly, the TBS-protected donor was stable to the TBAF workup conditions and **3** was obtained in good yield. The method is also highly suitable for the synthesis of oligosaccharides that possess repeating C2 glycosidic linkages due to the deprotection of the product glycosides. Glycoside **2** was tethered to glucose sugar silane using $B(C_6F_5)_3$ in 68% yield and subsequently glycosylated in 89% yield to give **4**.

The method was shown to tolerate more hindered tertiary alcohols. The dehydrogenative silylation was efficient with both sugar silanes using $B(C_6F_5)_3$ as the catalyst. The glycosylation provided α-glucoside **5** and β-mannoside **6** in good yield. The method was also applied to the synthesis of disaccharides as demonstrated by the synthesis of α-glucoside **7** as a single diastereomer. While the majority of the work

towards the dehydrogenative silylation of alcohols using C2 sugar silanes was performed by Zack, I contributed to the synthesis and characterization of glycosides **1-4** within this series.

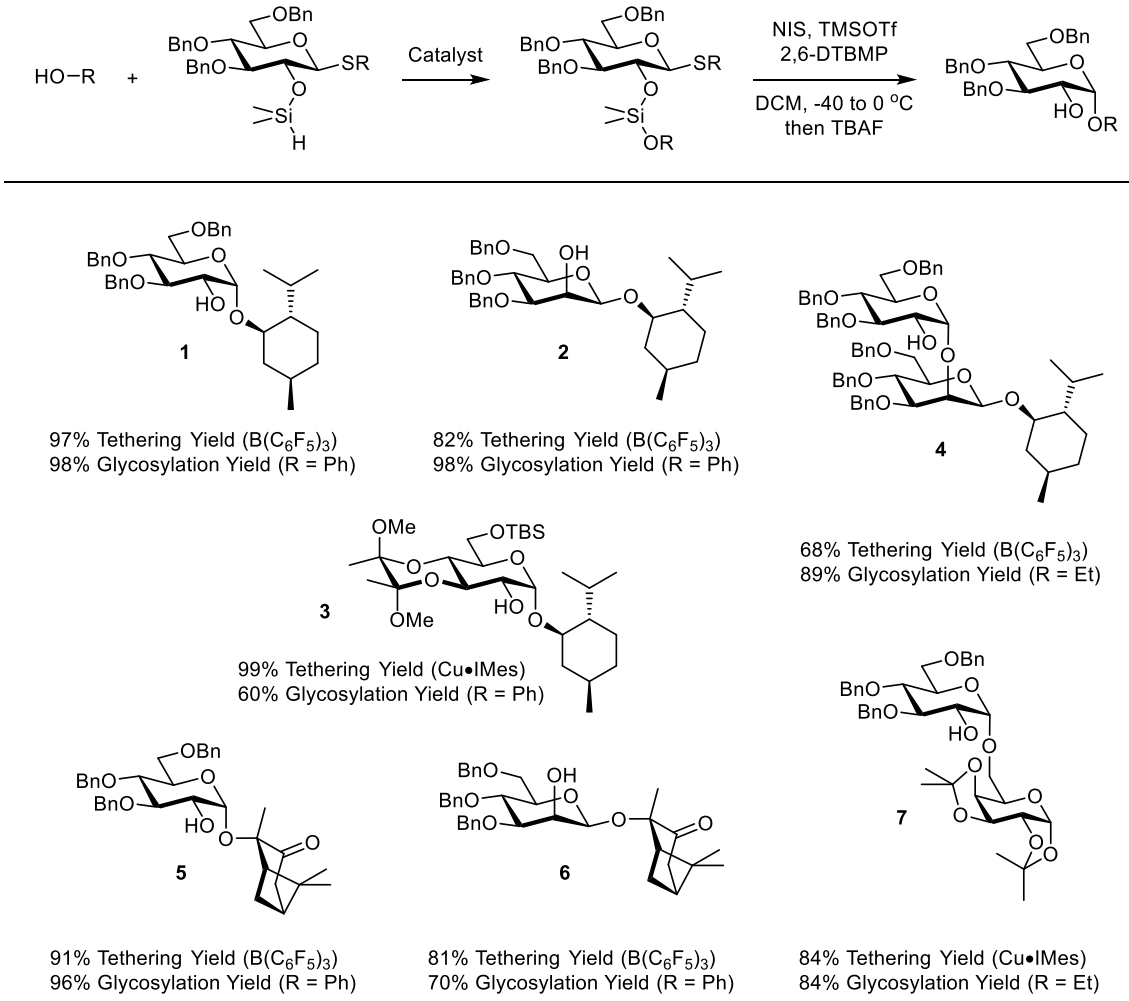


Table 2.1 – Glycosides Using Sugar Silanes in Dehydrogenative Silylations

Chapter 3
Sugar Silanes and C6 Delivery

3.1) Glucose and Mannose C2 Sugar Silanes

Previous work by Stork and Bols towards the synthesis of 1,2-*cis* glycosides via intramolecular aglycone delivery focused on the use of dimethylsilyl ketals as the tethering group. The use of dichloromethane to access tethered intermediates suffers from the use of bis-electrophilic dichlorodimethylsilane which is susceptible to the formation of homodimer byproducts. The Montgomery lab envisioned the use of sugar silanes as suitable reagents for the catalytic dehydrogenative silylation of alcohols to provide a more efficient route to the requisite intermediates for intramolecular aglycone delivery.

Working alongside Zach Buchan, my initial efforts in the Montgomery group focused on the synthesis and characterization of glycosides using C2 sugar silanes (Table 3.1). Both copper-IMes and $B(C_6F_5)_3$ were used to catalyze the dehydrogenative silylation of alcohols. This work included the synthesis of a variety of menthol glycosides to give both α-glucoside **1** and β-mannoside **2**. Furthermore, a sugar silane with both a silyl ether and cyclic acetal protecting group was shown to efficiently provide α-glucoside **3**. Iterative α-glucoside **4** was synthesized using **2** as the glycosyl acceptor.

In addition to the dehydrogenative silylation of alcohols, the dehydrogenative silylation of diols was explored using the $B(C_6F_5)_3$ catalyst. While the reaction of

$B(C_6F_5)_3$ is slower with primary alcohols due to catalyst inhibition, it has been shown to be quite selective for primary alcohols over secondary alcohols.[82] The use of $B(C_6F_5)_3$ with pyranoside glycosyl acceptors provides site selectivity for the primary C6 hydroxyl over unprotected secondary alcohols. Gratifyingly, the use of both glucose and mannose glycosyl acceptors with free hydroxyls at both the C4 and C6 positions resulted in the efficient formation of glycosides **8** and **9**. This strategy also worked for the synthesis of a cyclic acetal protected mannoside without protection at the C2 and C6 hydroxyls to give α-glucoside **10** in good yield.

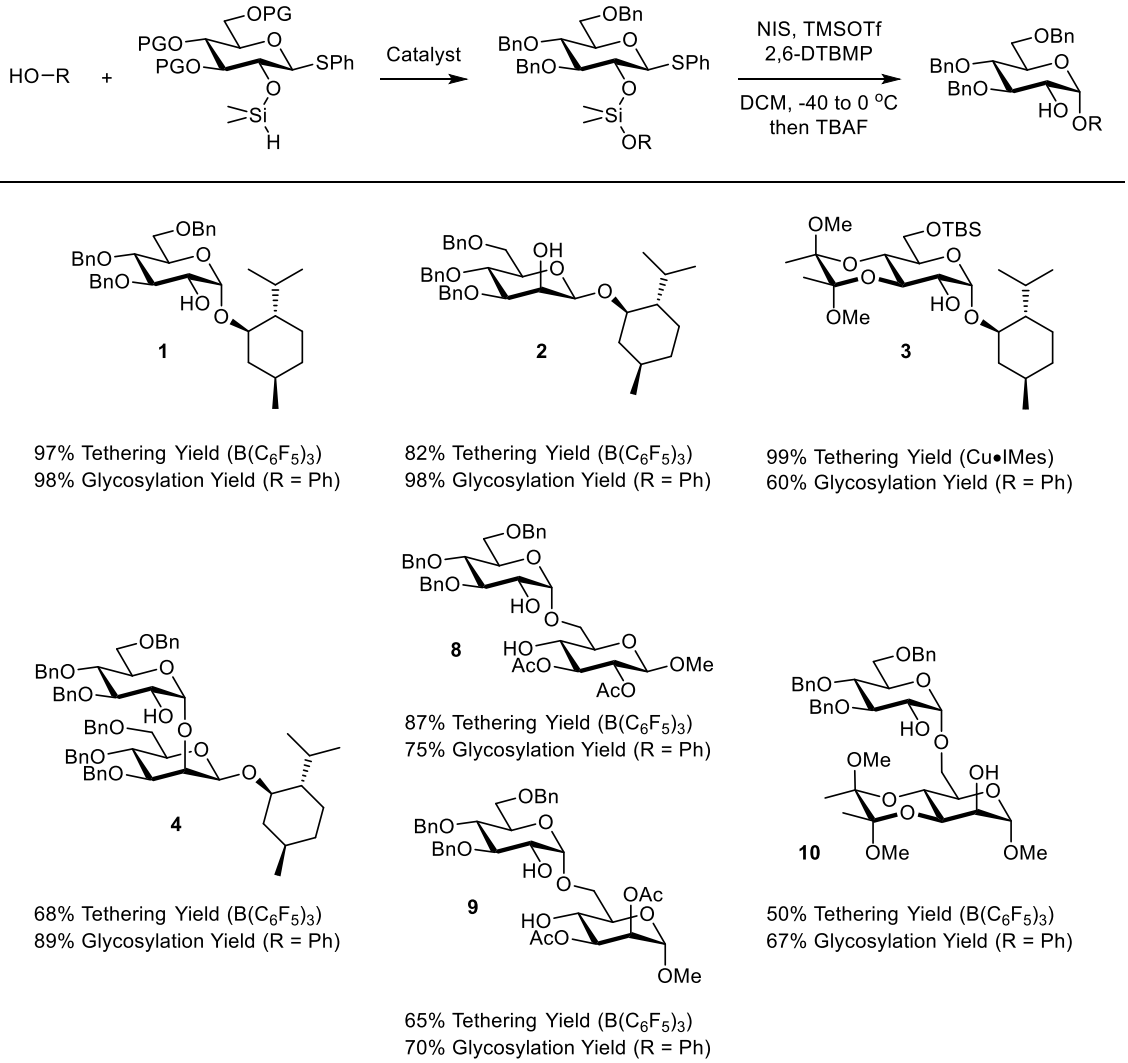


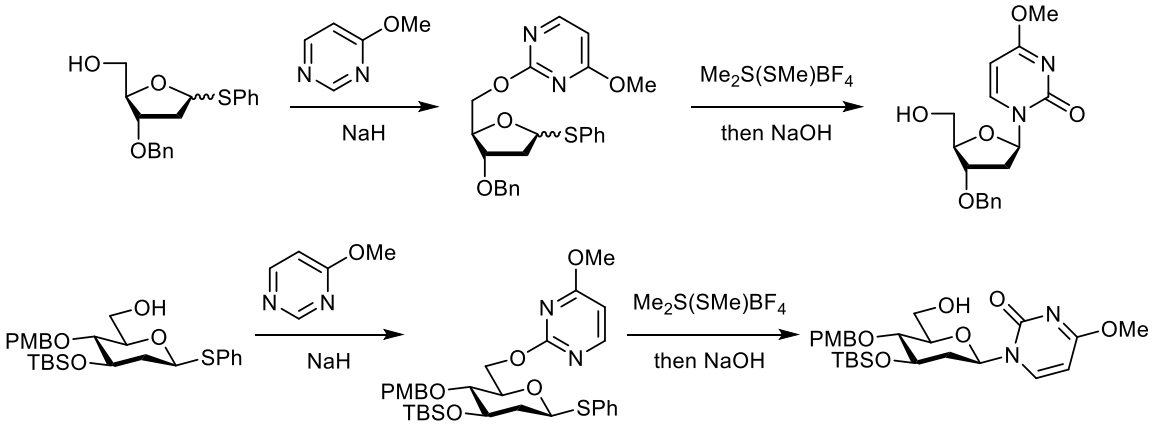
Table 3.1 – Contributions to C2 Sugar Silane Scope

3.2) Background and Strategy towards 1,2-*Trans* Glycosides via IAD

Sugar silanes efficiently provide difficult 1,2-*cis* glycosidic bonds while also taking advantage of silicon-hydride functionality for the hydrosilylation of ketones, reductive coupling of aldehydes and alkynes, and dehydrogenative silylation of alcohols; however, the constraints of intramolecular aglycone delivery from the C2 position limit the possible products to α-glucosides and β-mannosides. While the synthesis of 1,2-*trans*

glycosidic bonds is often an easier task, the potential for chemo- and site selectivity using sugar silanes provides motivation for the development of methodology to obtain 1,2-*trans* glycosides intramolecularly.

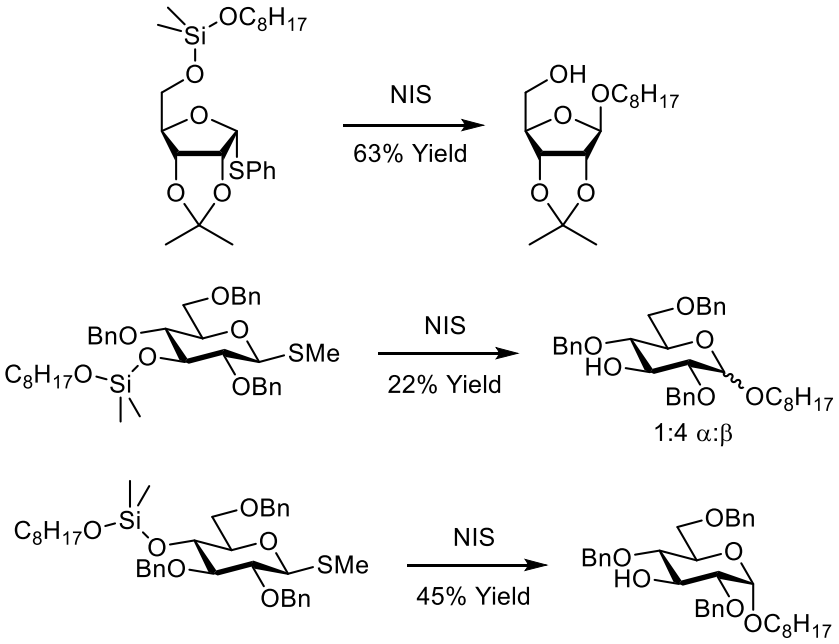
The tethering of aglycones to distal hydroxyl groups for intramolecular aglycone delivery has been previously reported. Sugimara developed a strategy to deliver pyrimidine bases by first tethering the base to the C5 hydroxyl of furanoside donors (Scheme 3.1).[84] Activation of the glycosyl donor resulted in an oxocarbenium cation that was trapped by the more basic nitrogen of the pyrimidine. Basic workup afforded the β-glycoside in good yield without any sign of the α-anomer. This strategy was later applied to the synthesis of β-pyranosides. Following a similar pathway, the same pyrimidine base could be delivered to obtain β-glycosides in good yield and stereoselectivity.[85]



Scheme 3.1 – C6 Delivery with Pyrimidine Bases

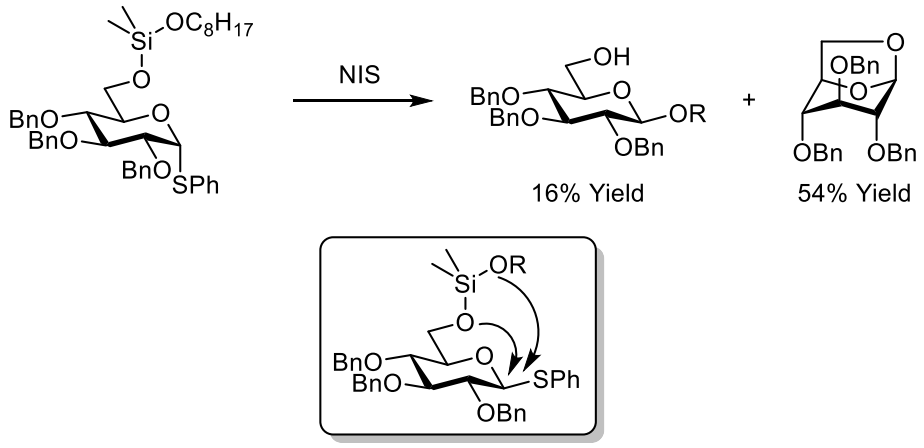
Bols has also studied silicon tethering at a variety of positions on furanoside and pyranoside donors using octanol as the glycosyl acceptor (Scheme 3.2).[86] Tethering to the C5 of a furanoside donor provides β-furanoside in moderate yield but with total stereoselectivity. Distal tethering in pyranosides was also explored. Tethering to the C3

hydroxyl of a thioglucosyl donor afforded 22% of an anomeric mixture favoring the β-glucoside. While the reaction did not show total stereoselectivity, the relatively high formation of β-glucoside indicates that some intramolecular glycosylation is occuring. On the other hand, tethering to the C5 hydroxyl provided the α-glucoside with total stereoselectivity and 45% yield, indicating that the intramolecular delivery is favored.



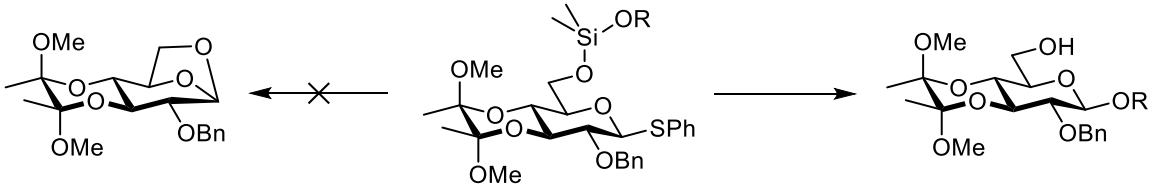
Scheme 3.2 – Silyl Tethers at Distal Hydroxyl Groups

Similar to the work of Sugimura[84,85], Bols studied the intramolecular delivery from the C6 position of a glycosyl donor. While the reaction provided 16% of the desired β-glucoside with total stereoselectivity, the major product from the reaction resulted from the addition of the C6 hydroxyl to the anomeric position to give bridged bicyclic product in 54% yield (Scheme 3.3). This is not surprising, as a variety of methods have been developed towards the synthesis of 1,6-anhydro sugars.[87] These products have also been shown to exist when glucose is subjected acidic conditions.[88]



Scheme 3.3 – Intramolecular Glycosylation from the C6 Hydroxyl

The ease of synthesis for 1,6-anhydro sugars indicates that the reaction is thermodynamically favorable. Conformationally, the pyran ring must be able to undergo a chair flip to bring the anomeric center close enough to the C6 hydroxyl for a reaction to take place. The use of a suitably rigidifying protecting group could preclude the formation of 1,6-anhydro byproducts. Since their discovery by Ley in the early 1990's, 1,2-diacetal protecting groups have been heavily used in carbohydrate chemistry for their simple installation, their ability to selectively mask 1,2-trans vicinal alcohols, and the conformational rigidity that they can lend to previously flexible structures.[89] We envisioned that the use of this protecting group could rigidify a glycosyl donor enough to allow intramolecular delivery of an aglycone tethered to the C6-hydroxyl without formation of the corresponding 1,6-anhydro product (Scheme 3.4).

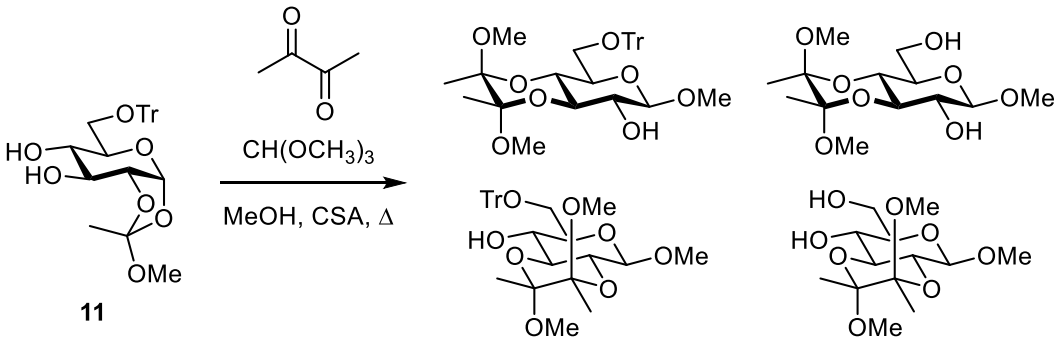


Scheme 3.4 - Strategy to Overcome 1,6-Anhydro Byproduct Formation

3.3) 2-Acetoxy and 2-Benzoyl Sugar Silanes

Synthesis of 2-Acetoxy C6 Sugar silanes

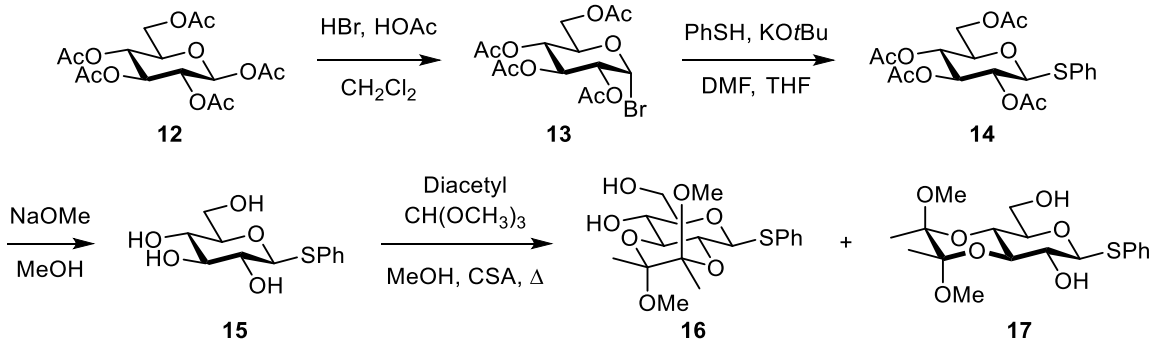
The synthesis of a glycosyl donor bearing a 1,2-*trans* diol began with known 1,2-orthoester **11**. The subjection of **11** to the acidic reaction conditions resulted in the deprotection of both the 1,2-orthoester and the C6 trityl group (Scheme 3.5). The unmasking of the 2-hydroxyl allowed the formation of both 2,3- and 3,4-protected regioisomers. Furthermore, the loss of the 1,2-orthoester resulted in the formation of the methyl glycoside. It was therefore determined that a different route should be explored, taking care that the protecting group strategy allows for the acidic conditions of the 1,2-*trans* diol protecting group.



Scheme 3.5 – Initial Attempt Towards 3,4-*Trans* Diol Protected Donor

The second attempt towards the synthesis of a 1,2-*trans* diol protected thioglycoside donor used the same conditions reported by Ley and followed a synthesis developed by Crich (Scheme 3.6).[90] Commercially available pentaacetate **12** was treated with hydrobromic acid and acetic acid in dichloromethane to give glycosyl bromide **13**. The addition of **13** to a solution of thiophenol and sodium *tert*-butoxide generated thioglycoside **14**, requiring only a recrystallization for purification. Subjection of **14** to

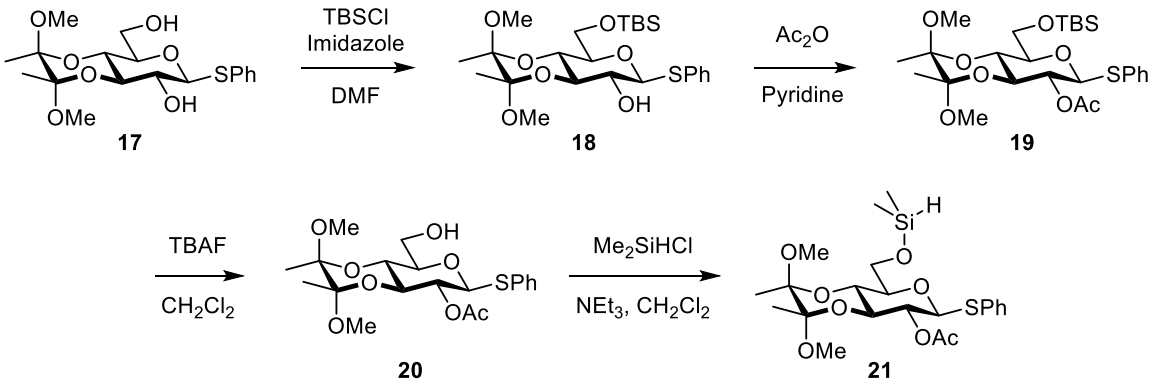
Zemplén deacetylation conditions gave deprotected **15** without any purification. Finally, **15** was treated with diacetyl, trimethyl orthoformate, and CSA to give a 1:1 ratio of regioisomers **16** and **17**. Thioglycoside **17** was easily separated from **16** via flash chromatography to give the regioisomerically pure compound.



Scheme 3.6 – Synthesis of 3,4-*Trans* Diol Protected Thioglucoside

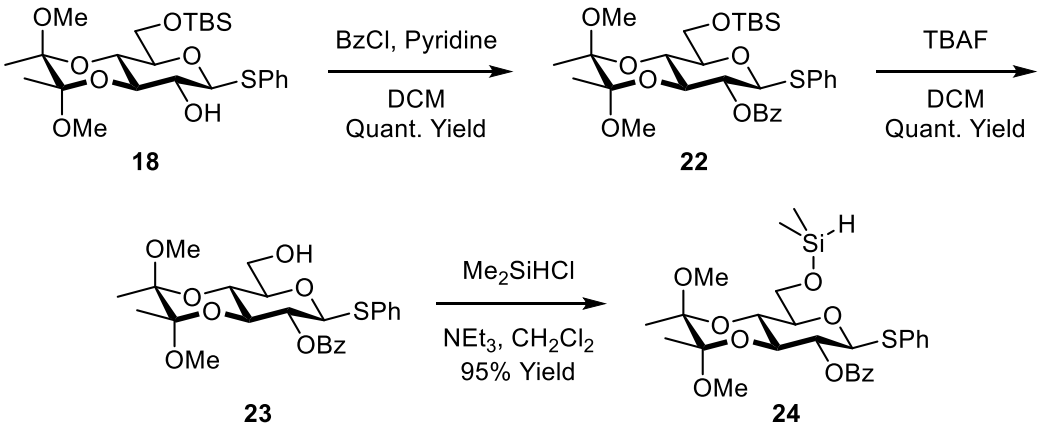
With the isolation of thioglycoside **17**, it was still necessary to protect the C2 hydroxyl with an acetate protecting group. This is a multistep process, since a primary-selective protecting group must first be used to protect the C6 hydroxyl. Subsequent acetylation of the C2 hydroxyl, followed by selective C6 deprotection, gives the desired thioglycoside **21** (Scheme 3.7). Given the precedent of using silyl ether protecting groups to selectively protect primary alcohols, **17** was treated with *tert*-butyldimethylsilyl chloride and imidazole in DMF to give selectively C6-protected **18** in 78% yield. The C2 hydroxyl of **18** was efficiently protected with an acetoxy group in 94% yield upon subjection to acetic anhydride and pyridine to give fully protected **19**. Access to the desired precursor **20** was then achieved in 80% yield by treating **19** with excess TBAF in dichloromethane. Following the published general procedure to make sugar silanes, **20** was treated with chlorodimethylsilane and triethylamine in dichloromethane to give sugar silane **21** in 98% yield. Like C2 sugar silanes, **21** is unstable to chromatography;

however, aqueous workup and evaporation of volatiles gives **21** in pure form. Long-term storage on the bench top results in hydrolysis of the silyl ether, yet **21** can be stored under vacuum indefinitely.



Scheme 3.7 – Synthesis of C2-Acetoxy Sugar Silanes

Benzoyl protecting groups at the C2 position are also able to participate in the oxocarbenium cation during a glycosylation. Since the use of a benzoyl protecting group would provide a sugar silane different in structure but similar in reactivity to C2-acetoxy sugar silanes, it also provides a convenient sugar silane which could be used in crossover type experiments. The synthesis of C2-benzoyloxy sugar silane 24 took three steps from the previously synthesized **18** and was very high yielding (Scheme 3.8). The subjection of **18** to benzoyl chloride and pyridine provided fully protected **22** in near quantitative yield. The silyl-ether deprotection of **22** also proceeded in quantitative yield to give **23**. Following the general procedure for sugar silane synthesis, **23** was suitably protected to afford sugar silane **24** in 95% yield.

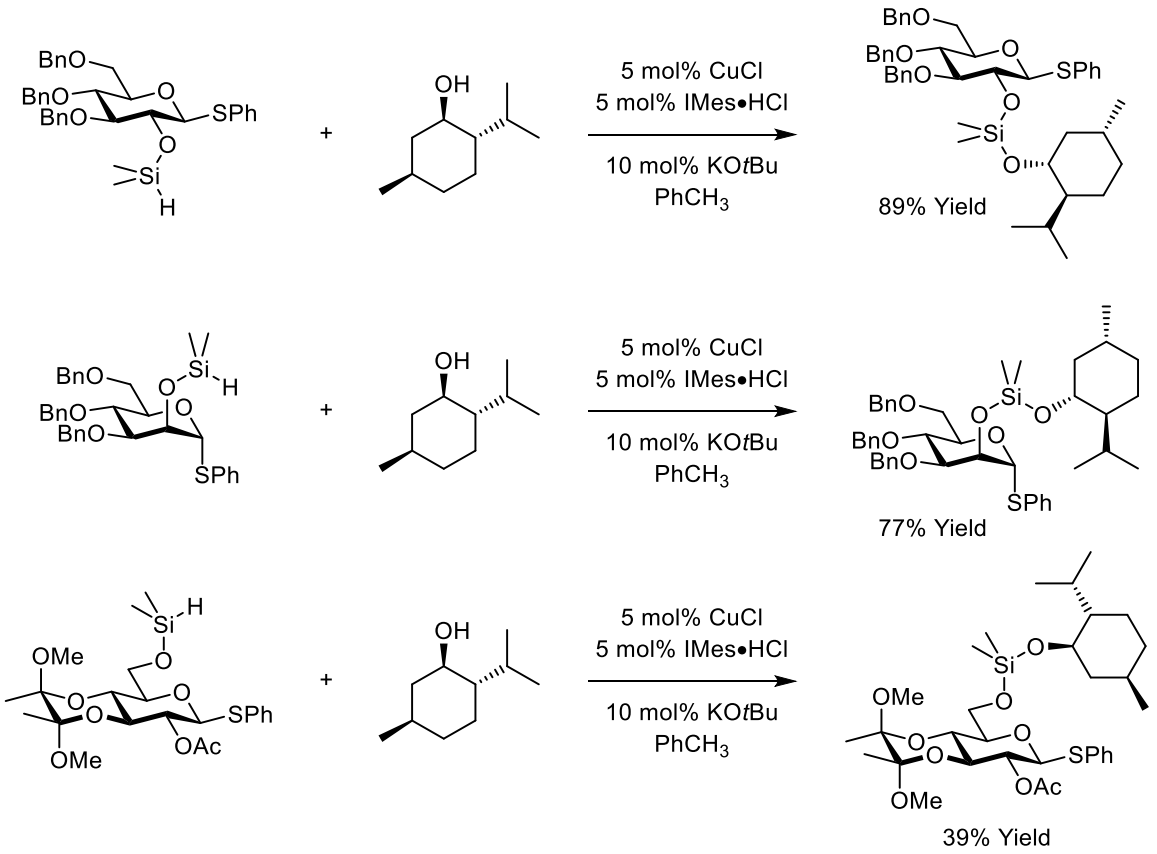


Scheme 3.8 – Synthesis of C2-Benzoyloxy Sugar Silanes

Dehydrogenative Silylation of 2-OAc Sugar Silanes

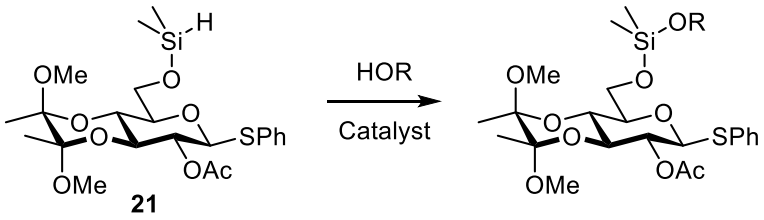
Before the ability of 2-acetoxy sugar silanes to undergo C6-delivery could be examined, the formation of the prerequisite tethered intermediates needed to be optimized. Previous work in our goup has shown that both $B(C_6F_5)_3$ and Cu•NHC catalyst give tethered intermediates from C2 sugar silanes and a variety of alcohols in high yield. These two catalysts, along with AuCl•Xantphos[91,92] and CuCl•Xantphos[93] catalysts which have shown activity for the dehydrogenative silylation of alcohols, were explored for their suitability with C6 sugar silanes and alcohols.

It was necessary to suitably develop a method for the synthesis of tethered intermediates using C6 sugar silanes. However, the copper-IMes catalyst that returned high yields using C2 sugar silanes was less efficient with C6 sugar silanes due to the hydrolysis of the more labile sugar silane. The dehydrogenative silylation of menthol using C2 glucose and C2 mannose sugar silanes returned yields of 89% and 77%, respectively. This yield of this reaction drops to 39% when 2-acetoxy sugar silane **21** is used (Scheme 3.9).



Scheme 3.9 – Comparison of C2 and C6 Sugar Silanes in Alcohol Silylation

The lower tethering yield of C6 sugar silanes using copper-IMes was not improved using less hindered alcohols. Butanol was silylated in only 44% yield using this catalyst. This led to the exploration of different catalysts to improve the tethering yields (Table 3.2). The use of Xantphos in place of IMes•HCl resulted in a further reduction in yield to 13%. A gold-Xantphos catalyst developed by Ito[91,92] gave no appreciable amount of the desired product. Finally, the use of $B(C_6F_5)_3$[94] as a Lewis acid catalyst gave the desired product in only 28% yield.



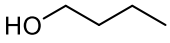
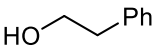
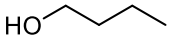
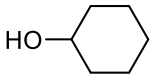
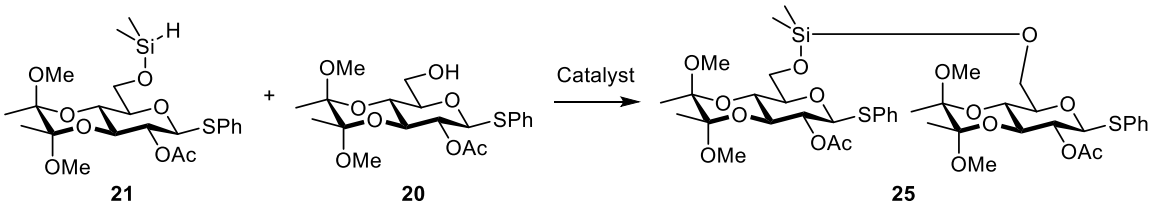
Catalyst	Alcohol	Yield
CuCl•IMes		44%
CuCl•Xantphos		13%
AuCl•Xantphos		n.r.
$B(C_6F_5)_3$		28%

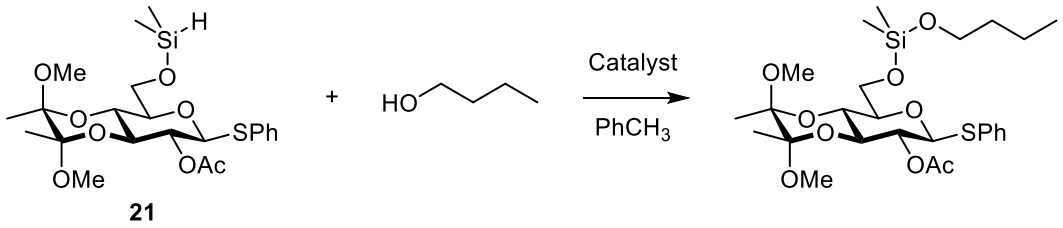
Table 3.2 – Initial Attempts Towards Dehydrogenative Silylation

Upon closer inspection of the byproducts formed during the dehydrogenative silylation of alcohols using C6 sugar silanes, it was found that a significant amount of the bis-silylated homodimer **25** is generated (Scheme 3.10). It's known that the hydrolysis of silyl ethers is slowed as the amount of steric bulk around the silicon center is increased. This is also true for the steric bulk centered on the parent alcohol carbon.[95] Considering that C2 dimethyl sugar silanes are already unstable to chromatography, it is perfectly reasonable for the even less sterically hindered C6 sugar silanes to be more susceptible to hydrolysis. If the silyl ether is in fact being hydrolyzed, the primary alcohol of **20** is now able to compete with the desired glycosyl acceptor. If **20** reacts with an equivalent of sugar silane **21**, two equivalents of the sugar silane have now been removed from the reaction. If a significant amount of homodimer **25** forms, there is too little sugar silane left in the reaction to react with the desired alcohol.



Scheme 3.10 – Formation of Homodimer

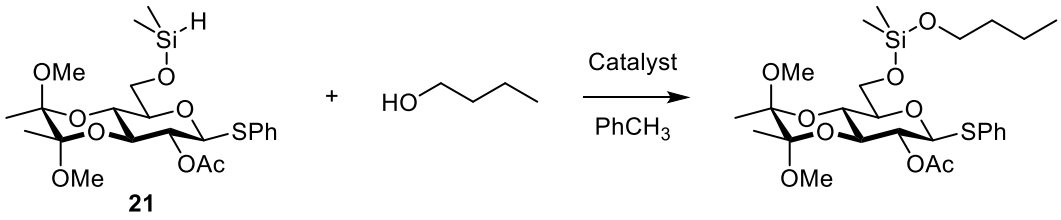
Since the formation of homodimer **25** is most likely caused by the hydrolysis of the C6 sugar silane under the conditions for dehydrogenative silylation, a few strategies were explored to overcome this challenge (Table 3.3). One was to prevent the hydrolysis from happening in the first place. In these initial reactions, butanol was chosen as an unhindered alcohol to reduce any complications of sterically hindered substrates. Since the hydrolysis only takes place under catalytic conditions, a lower catalyst loading might improve the yield. Unfortunately, the use of 1 mol% copper-IMes decreased the yield to 27%. The reaction at 0 °C returned a yield of 38%, as the decrease in temperature had no effect on the decomposition of the silane. Original reports by Nolan found that IPr is the most efficient NHC ligand for the hydrosilylation of ketones.[96,97] Additional, sodium *tert*-butoxide provides better yields than potassium *tert*-butoxide. The use of these conditions resulted in a modest increase in the yield to 48%; however, the consistency of the yields improved and these conditions were used moving forward.



mol% CuCl	mol % IMes•HCl	mol% KO*t*Bu	% Yield
5	5	10	44
1	1	2	27
5	5	10	38 (0 °C)
5	5 (IPr•HCl)	10 (NaO*t*Bu)	48

Table 3.3 – Initial Screening of Silylation Conditions

The amount of IPr•HCl used to make the catalyst has a large effect on the tethering yields (Table 3.4). It was ultimately a serendipitous result that was the key to optimizing the reaction so that C6 silyl-linked intermediates could be accessed efficiently. While weighing out the catalyst in the glovebox, 50% more IPr•HCl was used than desired. Interestingly, the yield using 7.5 mol% of IPr•HCl improved from 48% to 57%. A further increase in ligand to 10 mol% raised the yield significantly to 86%. Increasing the amount of NaO*t*Bu to 15 mol% lowered the yield to 68%. It was therefore a catalyst derived from 5 mol% CuCl, 10 mol% IPr•HCl, and 10 mol% NaO*t*Bu that was chosen as the optimized procedure.



mol% CuCl	mol % IPr•HCl	mol% NaO*t*Bu	% Yield
5	5	10	48
5	7.5	10	57
5	10	10	86
5	10	15	68

Table 3.4 – Further Optimization Using IPr•HCl as Ligand

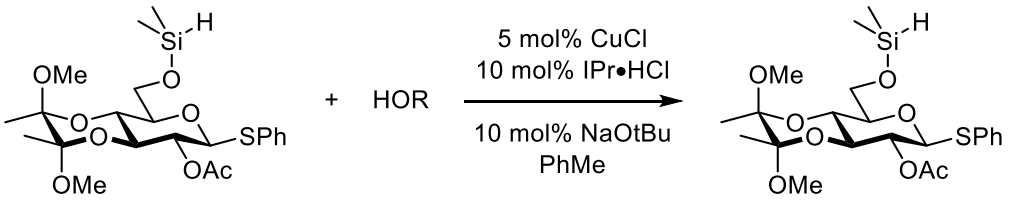
It was not immediately clear why the use of an additional equivalent of IPr•HCl results in such a significant increase in yield. It is proposed by Nolan that *tert*-butoxide serves two roles in the reaction mechanism.[81] An initial deprotonation of IPr•HCl gives the carbene IPr which can ligate CuCl to give CuCl•IPr. The second equivalent of *tert*-butoxide is next used to displace chloride to give the precatalyst CuO*t*Bu•IPr which can undergo sigma-bond metathesis with a sacrificial silane to give the active catalyst CuH•IPr.

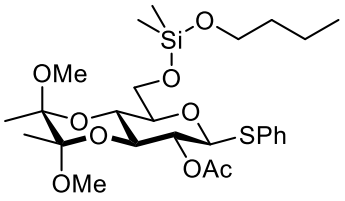
Scheme 3.11 – Formation of Active Catalyst

Cationic $[Cu(NHC)_2]X$ (X = PF_6 or BF_4) complexes have been isolated and their activity in the hydrosilylation of ketones explored.[96,97] Nolan showed that these

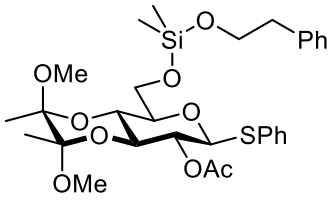
complexes actually give faster reaction times than their previously reported Cu•NHC catalysts. Additionally, they found that of fourteen different NHC's studied, IPr•PF_6 and IPr•BF_4 are by far the most efficient ligands. Mechanistic studies indicate that the mono-NHC ligated complex is still the active catalyst in the reaction. The improvement in reaction times is attributed to the additional equivalent of deprotonated NHC being a better facilitator of the sigma-bond metathesis between CuOR and SiH than *tert*-butoxide. This reconciles the fact that IPr•HCl gives the most productive results for the dehydrogenative silylation of alcohols. The additional equivalent of NHC likely increases the reaction rate such that it is better able to outcompete the hydrolysis of the sugar silane. While it is surprising that the yield was decreased with 15 mol% NaO*t*Bu, the higher yields indicate that there is possibly an equilibrium involved where at least some of the additional NHC is deprotonated. Furthermore, decomposition of the sugar silane may be exacerbated by the additional base.

A variety of alcohols were explored for their suitability with the newly optimized procedure (Table 3.5). Primary alcohols underwent the procedure in efficient yields. The tethered products of butanol (**26**) and phenethyl alcohol (**27**) were isolated in 86% and 75% yields, respectively. Simple secondary alcohols are also suitable for the method, as cyclohexanol was tethered to give **28** in near quantitative yields. Menthol was silylated in 78% yield to afford **29**, showing that even particularly hindered secondary alcohols could undergo the reaction. Finally, 2-benzyloxy sugar silane **24** was tethered to butanol to provide **30** in 86% yield.

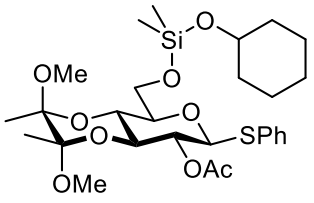




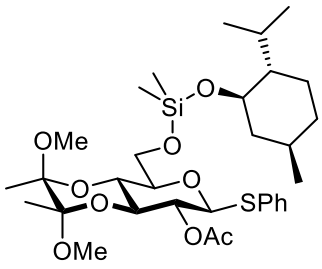
26, 86% Yield



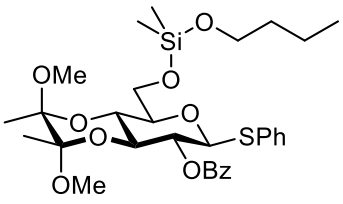
27, 75% Yield



28, 97% Yield



29, 78% Yield



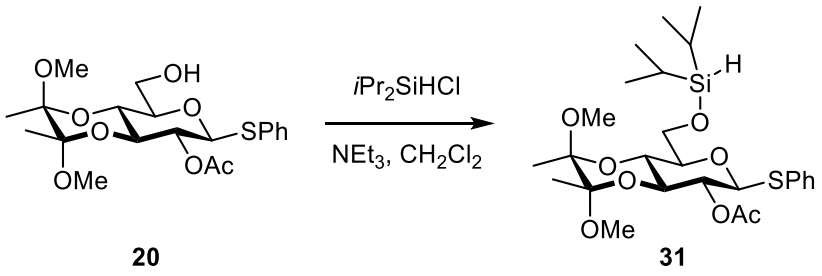
30, 86% Yield

Table 3.5 – Scope of Silylations with C2-Acetoxy and C2-Benzoyloxy Silanes

The use of a dimethylsilane functional handle in sugar silanes has the disadvantage of making them unstable to chromatography and for storage on the bench top. The use of a more sterically hindered dialkylsilane could improve the usability of the reagents by improving their stability and making them suitable for commercial sale. Previous work in our group has shown that many bulky dialkylsilanes are unsuitable for intramolecular aglycone delivery, but diisopropyl sugar silanes have shown particular promise. In addition to providing bench top stability, C2 diisopropyl sugar silanes have

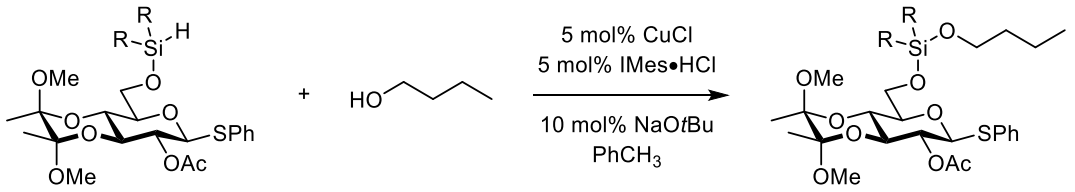
been shown to tolerate intramolecular aglycone delivery. Diisopropyl silanes were therefore chosen to explore the use of bulkier silanes with C6 delivery.

Exploration of C6 diisopropyl sugar silanes began with the synthesis of the diisopropyl analog. Similarly to dimethyl sugar silanes, precursor **20** was treated with *i*Pr_2SiHCl and NEt_3 in dichloromethane to give sugar silane **31** which was stable to flash chromatography (Scheme 3.11). The dehydrogenative silylation of butanol using sugar silane **31** returned a similar yield as the dimethyl analog (Table 3.6). Unlike the use of diisopropyl C2 sugar silanes, diisopropyl C6 sugar silanes were unsuitable for intramolecular aglycone delivery and were not further explored. The glycosylation likely failed due to the additional steric bulk on the silane.



20 **31**

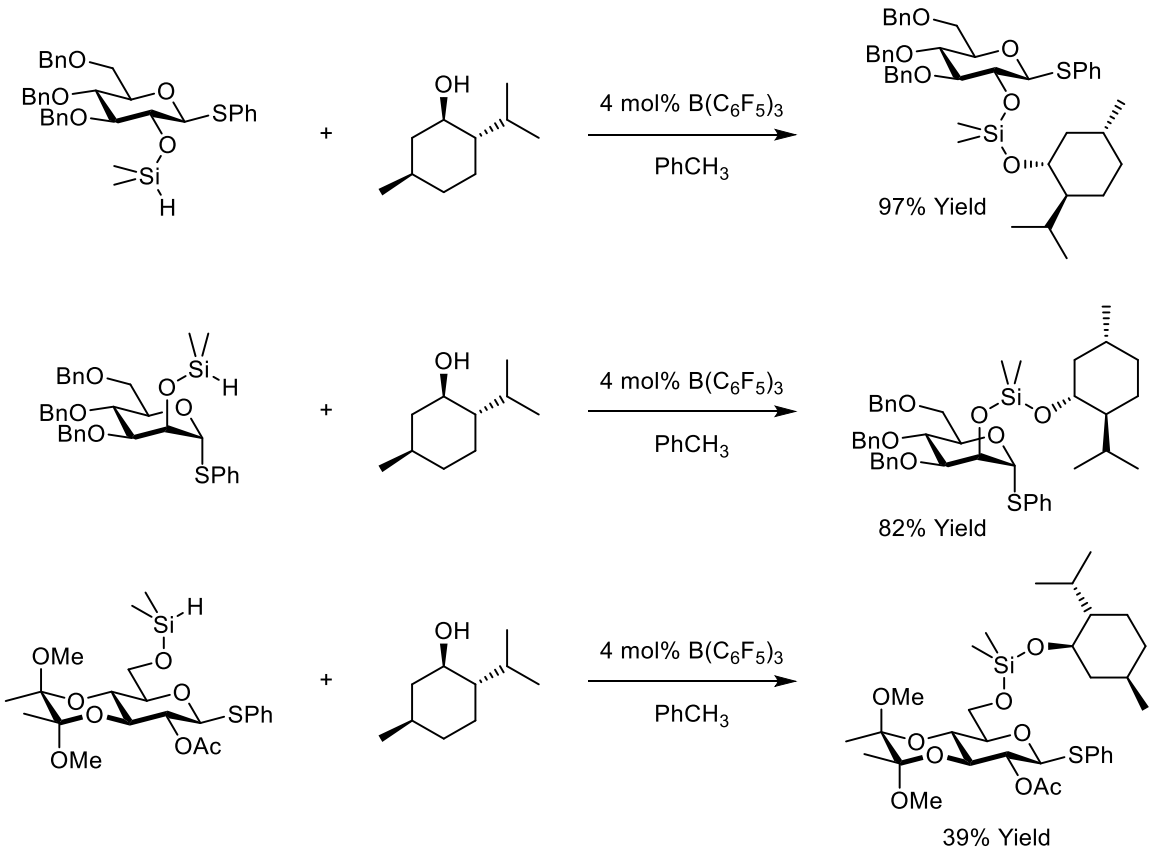
Scheme 3.12 – Synthesis of Diisopropyl C6 Sugar Silanes



R Group	% Yield
Me	44
*i*Pr	48

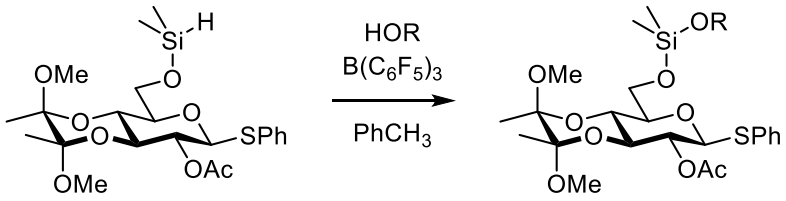
Table 3.6 – Comparison of Dimethyl and Diisopropyl C6 Sugar Silanes

In the late 1990's, the lab of Warren Piers developed methodology for the catalytic dehydrogenative silylation of alcohols using commercially available $B(C_6F_5)_3$. This catalyst has the advantage of being tolerant to a variety of functional groups. While competitive carbonyl hydrosilylation is possible using CuCl•NHC, $B(C_6F_5)_3$ is highly efficient with a variety of aldehydes, ketones, and esters. This catalyst has also been used for the dehydrogenative silylation of alcohols with C2 sugar silanes in high yield. Unfortunately, the success of $B(C_6F_5)_3$ with C2 sugar silanes did not immediately translate to C6 sugar silanes due to decomposition of the silane (Scheme 3.13). Like the initial efforts using the copper-IMes catalyst, the use of $B(C_6F_5)_3$ resulted in lower yields and significant amounts of homodimer **25** formation.



Scheme 3.13 – Comparison of C2 and C6 Sugar Silanes Using $B(C_6F_5)_3$

Two strategies were developed to overcome the hydrolysis of C6 sugar silanes using $B(C_6F_5)_3$ as catalyst (Table 3.7). First, slow addition to a mixture of alcohol and catalyst would keep the relative concentration of sugar silane low such that the formation of homodimer **25** would be less likely. Additionally, the temperature of the reaction could have an effect on the yield. Gratifyingly, the slow addition at room temperature increased the yield from 39% to 65%. Although cooler temperatures could have slowed the rate of silane decomposition to improve the yield, only a reduction in yield was observed. On the other hand, warming the reaction returned a modest improvement in yield. Slow addition of the silane at 40 °C improved the yield further to 78%. These conditions were tested with another secondary alcohol and a similar increase in yield was found.



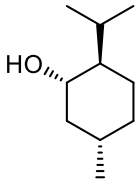
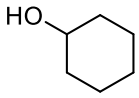
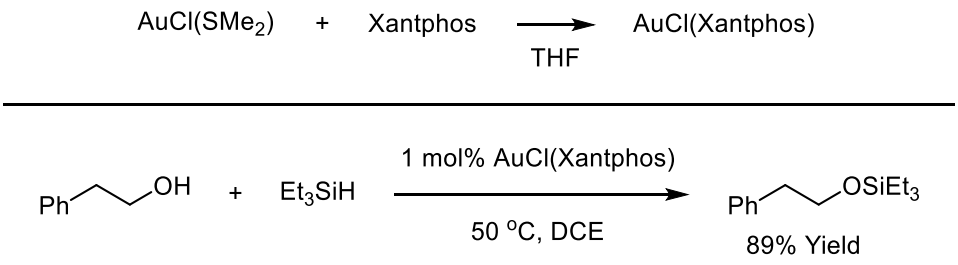
HOR	Temp	Conditions	% Yield
	rt	---	39
	rt	Slow Addition	65
	0 °C	Slow Addition	39
	40 °C	Slow Addition	72
	60 °C	Slow Addition	68
	rt	---	28
	40 °C	Slow Addition	56

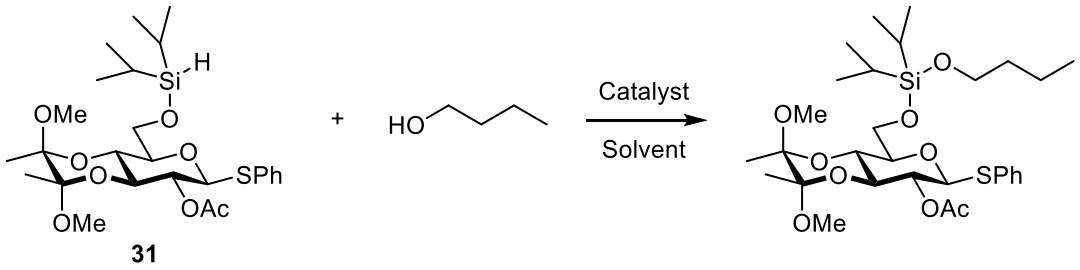
Table 3.7 – Optimization of C6 Sugar Silanes Using $B(C_6F_5)_3$

A reoccurring challenge using C6 sugar silanes for the dehydrogenative silylation of alcohols is the formation of homodimer **25**. This is particularly difficulty to overcome using $B(C_6F_5)_3$ as the catalyst. Piers reported slower reaction times using primary alcohols as substrates due to the more nucleophilic primary alcohols being a better inhibitor of the catalyst. Regardless of the nature of the intended alcohol to undergo dehydrogenative silylation, the hydrolysis of sugar silanes reveals a primary alcohol that can inhibit the catalyst as well as compete with the desired alcohol. This problem will likely continue to plague the use of C6 sugar silanes as long as they are limited to the hydrolysis-susceptible dimethyl variants.

A brief amount of time was spent exploring the use of a gold-phosphine catalyst for the dehydrogenative silylation of alcohols developed by Ito.[91,92] This catalyst has been shown to tolerate a variety of functional groups including acids, ketones, aldehydes, and halogens, and displays great site selectivity by highly preferring primary alcohols over secondary alcohols. Furthermore, gold-Xantphos has been shown to tolerate particularly hindered silanes. As diisopropyl sugar silanes were at the time being explored, it was these silanes that were tested with this new catalyst. An *in situ* generated catalyst was first used, but it was found that the reaction of sugar silane **31** with butanol at 50 °C generated no product formation (Table 3.8). The discrete catalyst Au(Xantphos)Cl was then synthesized to see if there is an improvement in yield (Scheme 3.14). Ensuring that the discrete catalyst had adequate reactivity, 1 mol% was shown to successfully promote the reaction of triethylsilane and phenethyl alcohol in 89% yield. Unfortunately, the same conditions using sugar silane **31** returned only a trace amount of the desired product. Raising the catalyst loading to 2 mol% improved the yield modestly to 20%. Further optimization was only able to improve the yield to 28% by using 5 mol% catalyst loading, using DMF as solvent, and heating the reaction to 80 °C. Similar to the dehydrogenative silylation of alcohols using other catalysts, a large amount of homo-dimer byproduct was generated, most likely due to hydrolysis of the sugar silane.



Scheme 3.14 – Synthesis of Discrete Catalyst



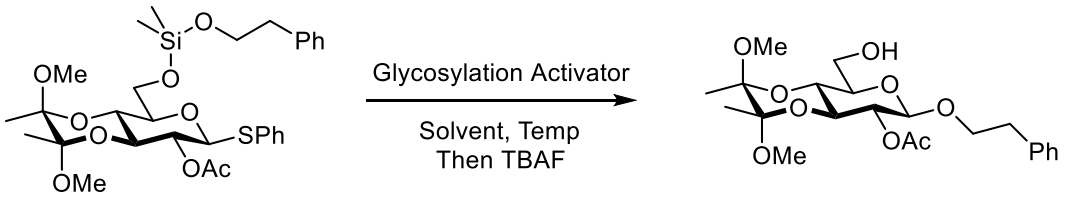
Catalyst	Solvent	Temperature	% Yield
5% $AuCl(SMe_2)$ + 5% Xantphos	DCE	50 °C	No Product
1% Au(Xantphos)Cl	DCE	50 °C	Trace
2% Au(Xantphos)Cl	DCE	50 °C	20
5% Au(Xantphos)Cl	DMF	80 °C	28

Table 3.8 – Dehydrogenative Silylation with Gold-Xantphos

Glycosylation of 2-Acetoxy C6 Sugar Silanes

With an efficient route to the requisite silyl-tethered intermediates in hand, attention next turned to their intramolecular glycosylation to give β-glycosides. There are a number of advantages to utilizing thioglycosides as glycosyl donors. The synthesis of thioglycosides is typically efficient and they can be accessed from a variety of other common glycosyl donors. Thioglycosides are very stable and tolerate a variety of reaction conditions necessary for protecting group manipulations during their syntheses. Despite their high degree of stability, thioglycosides can be easily activated through the use of thiophilic electrophiles. Additional precaution must be taken to use thioglycosides as the glycosyl donor of sugar silanes; since many thioglycoside activators can generate Brønsted acid, a non-nucleophilic base is typically added to avoid decomposition of the dimethylsilyl tethering group.

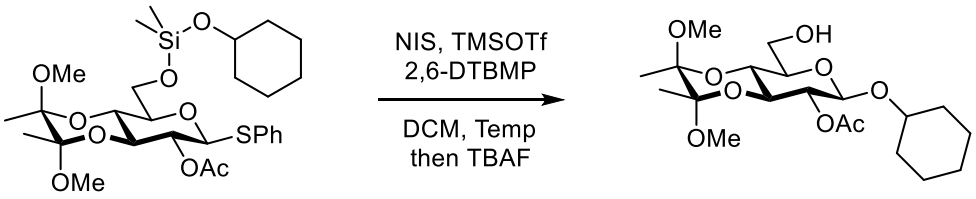
A variety of glycosylation activators were studied for their ability to successfully provide β-glycosides through C6 delivery (Table 3.9). A simple primary alcohol, phenethyl alcohol, was chosen as the glycosyl acceptor. Methyl triflate was first examined for its ability to activate the glycosyl donor, but poor activation took place even at room temperature and none of the desired product was detected. DMTST, generated *in situ* by the reaction of S_2Me_2 and MeOTf, has been developed as an efficient activator for thioglycosides.[98,99] The use of DMTST and 2,6-DTBMP with C2 sugar silanes has provided moderate glycosylation yields. However, the use of DMTST with C6 sugar silanes returned only a 28% yield. A large number of thioglycoside activators work best at lower temperatures, so DMTST was added at -40 °C and the reaction was warmed to 0 °C. However, the lower temperatures resulted in a decrease of the yield. Finally, it was found that the use of NIS and TMSOTf at lowered temperatures promote the glycosylation in 76% yield. In general, NIS-TSMOTf provides the best glycosylation yields regardless of the donor or accepter that is used.



Catalyst	Solvent	Temperature	% Yield
5 equiv. MeOTf	Diethyl Ether	rt	No Dsd Pdt
4 equiv. $(SMe)_2$ 3.6 equiv. MeOTf 2 equiv. 2,6-DTBMP	DCM	rt	28%
4 equiv. $(SMe)_2$ 3.6 equiv. MeOTf 2 equiv. 2,6-DTBMP	DCM	-40 °C to 0 °C	22%
1.3 equiv. NIS 1.2 equiv. TMSOTf 2 equiv. 2,6-DTBMP	DCM	-40 °C to 0 °C	76%

Table 3.9 – Optimization of Thioglycoside Activator

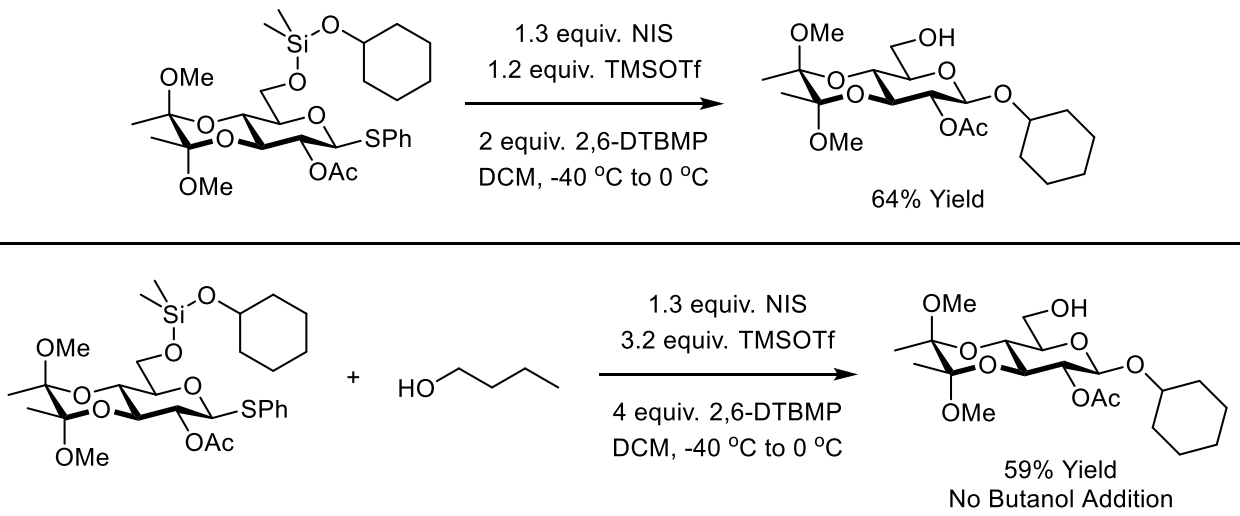
An increase of steric bulk on the glycosyl acceptor is met with a decrease in the glycosylation yield (Table 3.10). Using the optimized procedure from above, the glycosylation yield with cyclohexanol as the glycosyl accepter is 64%. An increase in temperature might have improved the intramolecular delivery with bulkier glycosyl acceptors, however addition of the glycosylation promoter at 0 °C instead of -40 °C returned the same yield. The reaction was also attempted at room temperature, however the yield was further reduced to 56%. Ultimately, a change in the reaction temperature had no positive effect and further manipulation was abandoned.



Temperature	% Yield
-40 to 0 °C	64%
0 °C	64%
rt	56%

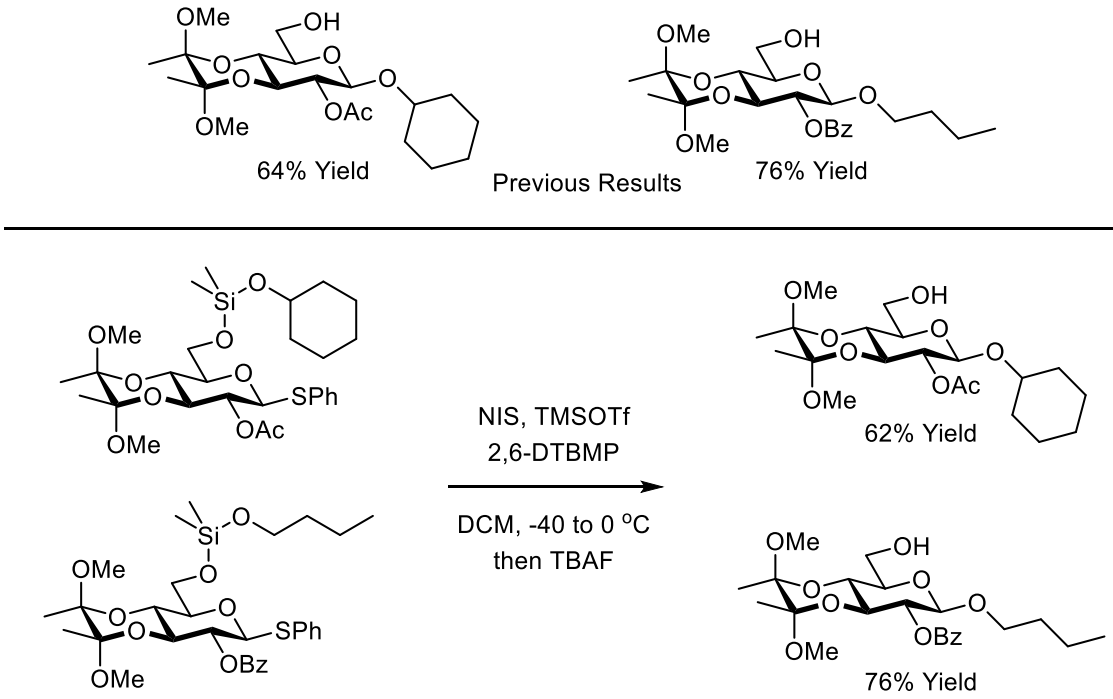
Table 3.10 – Temperature Effect on the Glycosylation

A variety of control experiments were performed to test the intramolecular nature of the glycosylation as well as the necessity of the *trans*-diol protecting group. Since glycosyl donors with C2-acetoxy groups would be expected to give 1,2-trans products in an intermolecular glycosylation, the formation of these products alone is not enough evidence to show that the reaction with sugar silanes is proceeding intramolecularly. To gauge if the reaction is in fact proceeding through an intramolecular mechanism, a glycosylation was carried out in the presence of an exogenous alcohol. Specifically, two equivalents of butanol were added to the cyclohexanol-tethered intermediate and the donor was activated (Scheme 3.15). Since two equivalents of butanol were added to the reaction, an additional two equivalents of TMSOTf were used to account for the silylation of the exogenous alcohol. There was no evidence of butanol acting as the glycosyl acceptor during the glycosylation and purification provided the cyclohexyl β-glucoside in roughly the same yield as previous experiments. The fact that there was no addition of butanol indicated that the reaction is likely proceeding through an intramolecular mechanism.



Scheme 3.15 – Control Experiment with Exogenous Alcohol

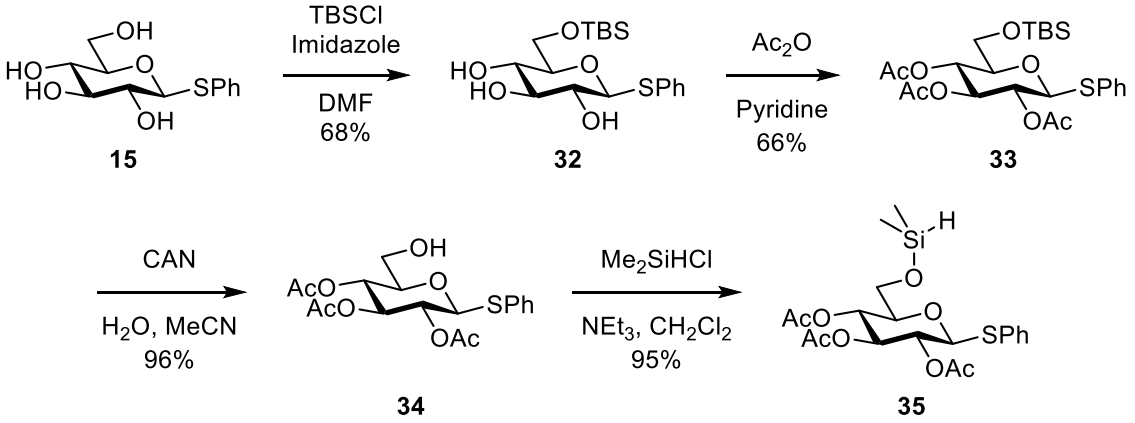
A crossover experiment was devised to further show that the glycosylation proceeds through an intramolecular mechanism. The unique participating characteristic of a glycosyl donor with a 2-acetoxy group requires that a structurally different donor with similar reactivity be designed. The 2-benzoyloxy sugar silane provides this similar reactivity to its C2-acetoxy analog. With these two thioglycoside donors in hand, tethered intermediates were synthesized bearing two different glycosyl acceptors so that crossover could be detected. The C2-acetoxy sugar silane was tethered to cyclohexanol while the C2-benzoyloxy sugar silane was tethered to butanol. The tethered intermediates were combined and treated with NIS-TMSOTf activator to give multiple products (Scheme 3.16). Only two glycoside products were formed in the reaction and there was no evidence of any crossover products.



Scheme 3.16 – 2-OAc and 2-OBz Crossover Experiment

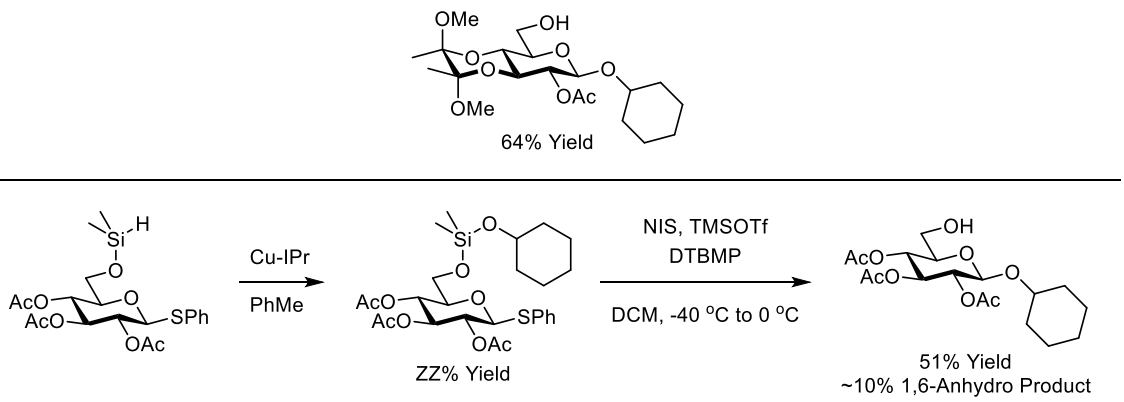
Results at this point had shown that the C5 delivery of glycosyl acceptors does in fact proceed intramolecularly, but the necessity of the 1,2-trans diol protecting group had not been explored. Since Bols carried out his initial experiments for C6 delivery with a donor containing a 2-benzyloxy group, it was still possible that the use of protecting groups at the C2 position which could participate in the oxocarbenium formation actually provide the ability to inhibit 1,6-anhydro byproduct formation. To test this, a 2,3,4-triacetoxy C6 sugar silane was synthesized (Scheme 3.17). Selective protection of the C6 hydroxyl was carried out using TBSCl, imidazole, and DMF in 68% yield to provide **32**. Compound **32** was treated with Ac_2O and pyridine to give fully protected **33**. A variety of methods were explored for the deprotection of the C6 silyl ether. The use of TBAF resulted in the migration of the C4 acetyl protecting to the C6 hydroxyl. Gratifyingly, the

use of CAN resulted in a very high yielding deprotection to give **34**. Finally, silane **35** was accessed in 95% yield using the general procedure.



Scheme 3.17 – Synthesis of 2,3,4-Triacetoxy C6 Sugar Silane

Sugar silane **35** was tethered to cyclohexanol using Copper-IPr to give **36** (Scheme 3.18). The glycosylation of **36** gave the desired β-glucoside in 51% yield with moderate formation of 1,6-anhydro byproduct. Interestingly, the switch from a C2-benzyloxy to a C2-acetoxy on the donor does in fact inhibit the formation of byproduct. While Bols saw 54% of the 1,6-anhydro byproduct using a primary glycosyl acceptor with his C2-benzyloxy donor, only ~10% was formed using the sugar silane **35**. Furthermore, this was accompanied by only a moderate decrease in yield. This indicates that while the C2-acetoxy group does have a significant impact on the reaction mechanism, the *trans*-diol protecting group is necessary to fully prevent the formation 1,6-anhydro byproducts.



Scheme 3.18 – Necessity of 1,2-Trans Diol Protecting Group

The intramolecular aglycone delivery using C6 sugar silanes with participating protecting groups at the C2 position works well with relatively unhindered glycosyl acceptors (Table 3.11). Butyl β-glucosides **38** and **39** were obtained using both C2-acetoxy and C2-benzoyloxy sugar silanes in 75% and 76% yields, respectively. Phenethyl β-glycoside **40** was obtained in 76% yield. Moderate decreases in yield are observed with secondary glycosyl acceptors, as cyclohexanol was glycosylated to give **41** in 64% yield. More sterically hindered secondary alcohols experience a significant decrease in the desired product and the glycosylation is accompanied by 1,6-anhydro byproduct **25** as well as the addition of succinimide. Menthol was glycosylated in only 21% yield to afford glycoside **42.** The decrease in yield is likely due to higher activation energy for the seven-membered transition as steric bulk is added to the silane or the aglycone. With this in mind, it makes sense that the similarly sterically encumbered diisopropyl C6 sugar silanes give no desired product upon activation. The reduced rate for C6 delivery provides an opportunity for the reactive oxocarbenium ion to interact with the C6 hydroxyl group or the succinimide from the activator.

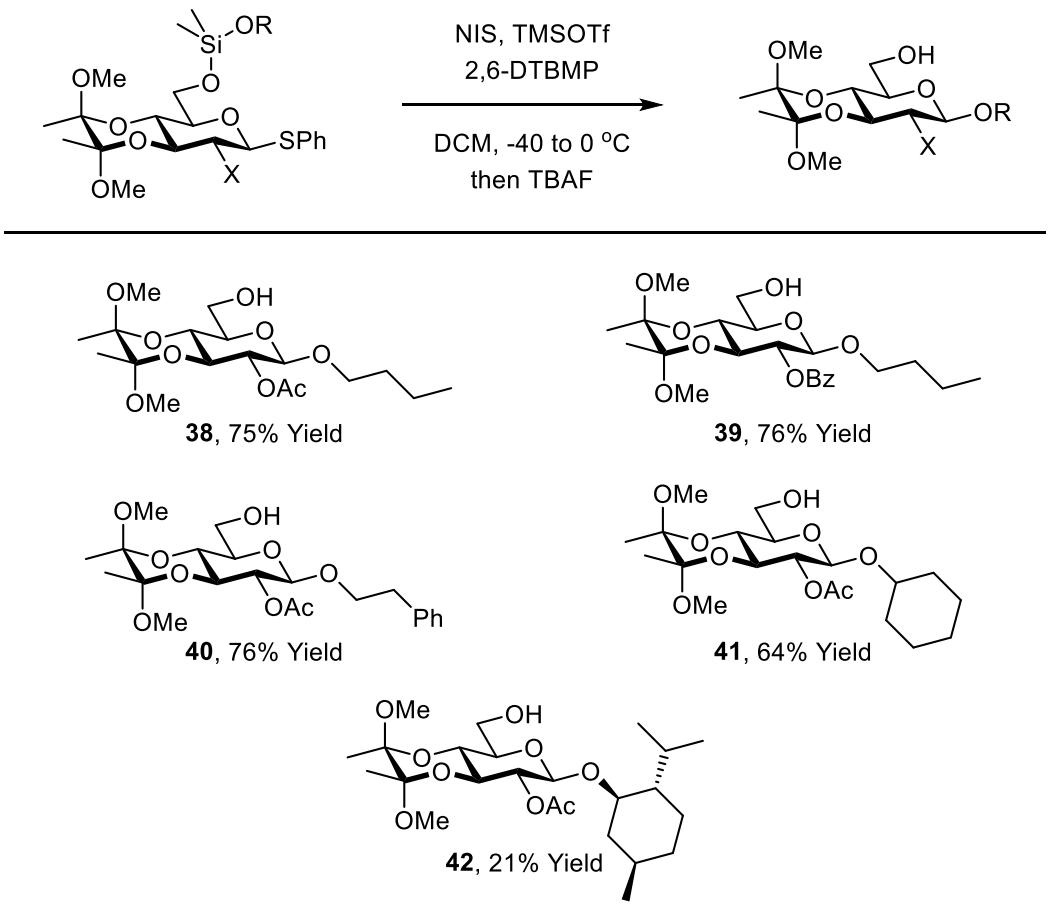


Table 3.11 – Glycosylation Scope of 2-Acetoxy and 2-Benzoyloxy Sugar Silanes

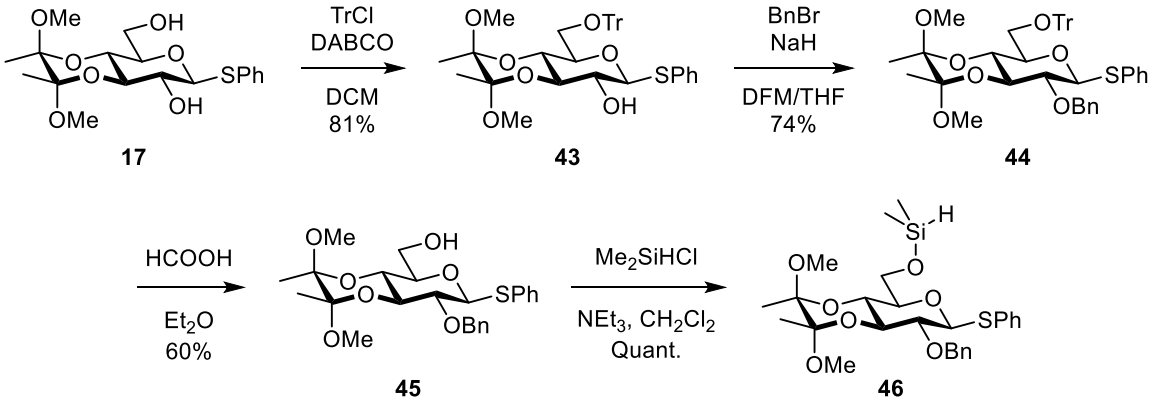
3.4) 2-Benzyloxy and 2-Azido C6 Sugar Silanes

The previous examples of intramolecular aglycone delivery have utilized either an acetoxy or a benzoyloxy group at the C2 position. While the glycosylations were shown to be completely stereoselective, similar selectivity could likely be obtained intermolecularly due to the participation of these protecting groups in the glycosylation mechanism. Alternatively, the synthesis of β-glucosides using non-participating protecting groups at the C2 hydroxyl can be challenging. Aside from a very sterically bulky protecting group, it is difficult to overcome the innate preference of incoming glycosyl acceptors for an axial approach due to the anomeric effect. Further development

of intramolecular aglycone delivery using C6 sugar silanes could provide a unique strategy to obtain β-glucosides in cases where a participating group on the C2 hydroxyl is either impossible or is inefficient.

Synthesis of 2-Benzyloxy Sugar Silanes

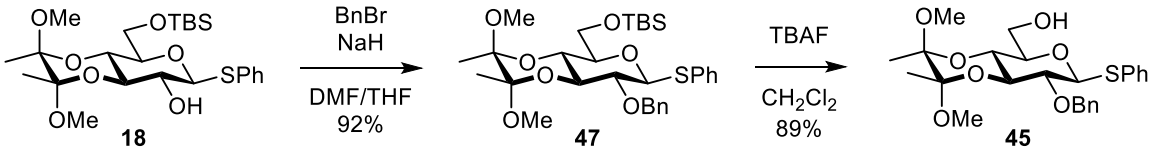
Initial attempts towards the synthesis of 2-benzoyloxy sugar silanes focused on the use of a trityl group for the selective protection of the C6 hydroxyl (Scheme 3.19). Diol **17** was treated with trityl chloride and DABCO in DCM to give trityl-protected **43** in 81% yield. This compound was then reacted with sodium hydride in the presence of benzyl bromide to give fully protected **44** in 74% yield. Deprotection of the trityl group was difficult and a variety of methods were tried. The treatment of **44** with formic acid in diethyl ether gave the best results and afforded **45** in 60% yield. Sugar silane **46** could then be obtained using chlorodimethylsilane and triethylamine in near quantitative yield.



Scheme 3.19 – Synthesis of 2-Benzyloxy Sugar Silanes

A much more efficient synthesis of **45** was later developed by utilizing a silyl ether protecting group for the C6 hydroxyl, similar to the synthesis of 2-acetoxy and 2-benzoyloxy sugar silanes (Scheme 3.20). Treatment of **18** with sodium hydride in the

presence of benzyl bromide and with the use of DMF as a cosolvent provided the fully protected **47** in 92% yield. Unlike the removal of the trityl group, deprotection of the silyl ether proceeded efficiently in 89% yield upon exposure to TBAF to provide **45**.



Scheme 3.20 – Improved Synthesis of 2-Benzyloxy Sugar Silanes

A variety of alcohols were silylated using the newly synthesized 2-benzyloxy C6 sugar silanes (Table 3.12). Primary alcohols were shown to work efficiently as butanol and phenethyl alcohol were silylated to give **48** and **49** in 90% and 72% yield, respectively. The method also worked with secondary alcohols, as the reaction with cyclohexanol proceeded in 73% yield to afford **50**. Compound **51** was obtained in 70% yield, as sterically encumbered menthol was efficiently silylated. The potential for iteratively synthesized glycosides was also explored. The synthesis of **52**, **53**, and **54** was lower yielding than with simple glycosyl acceptors. To combat the lower yields, 1.5 equivalents of sugar silane could be used in the reaction. The desired silyl tethered intermediates could be difficult to obtain in pure form due to the formation of homodimer byproducts; However, it was later shown that impure mixtures of tethered intermediates and homodimer are suitable for the glycosylation and, assuming enough glycosylation promoter is used, the presence of homodimer byproducts do not impact the yield of the transformation.

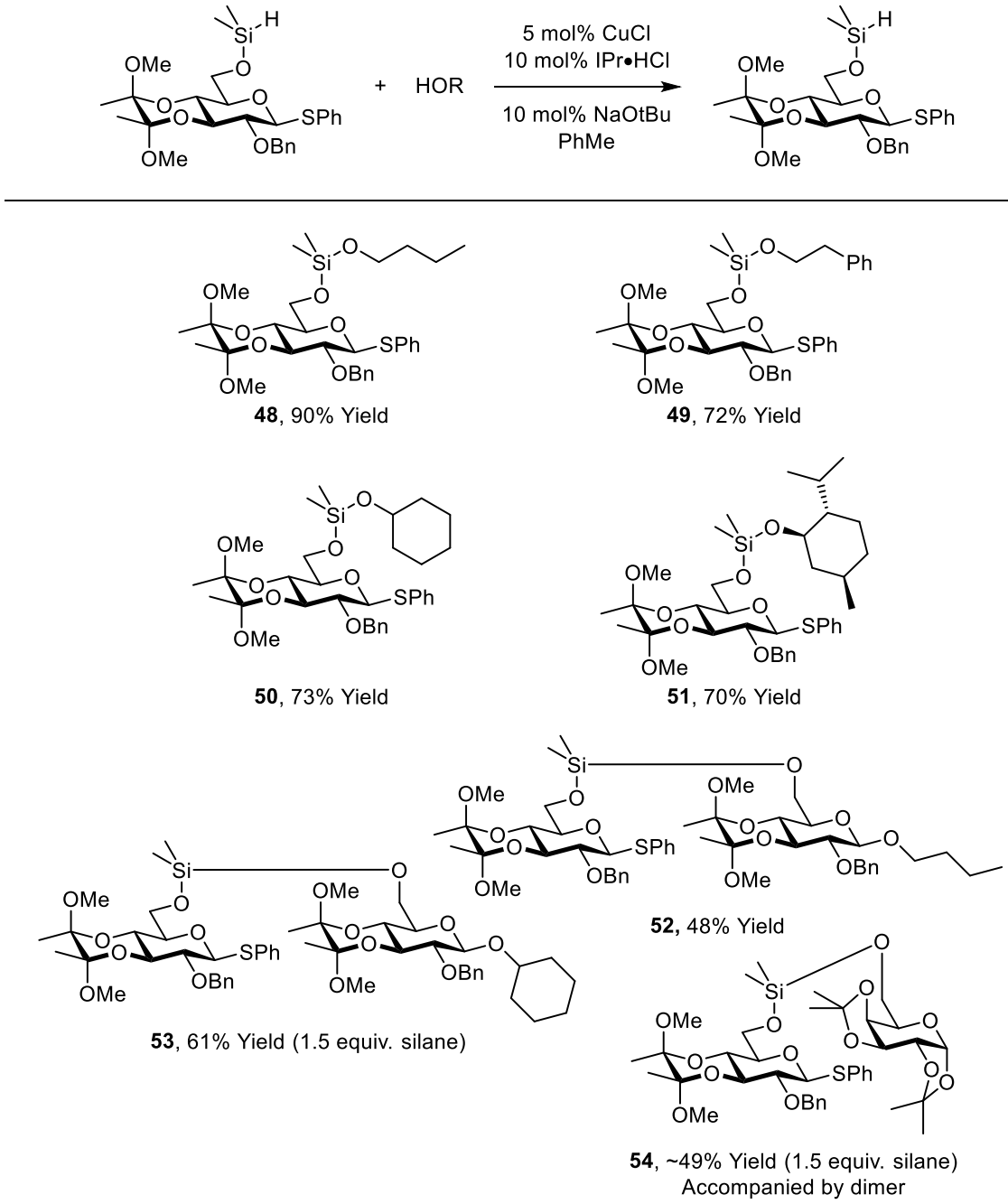


Table 3.12 – Scope of Alcohol Silylations with C2-Benzyloxy Sugar Silanes

The use of $B(C_6F_5)_3$ as the catalyst for the dehydrogenative silylation of alcohols using C2-benzyloxy sugar silanes was also explored (Table 3.13). This catalyst is particularly well suited for the silylation of secondary alcohols, as the reaction rate is

improved compared to that of primary alcohols due to catalyst inhibition. Using slow addition, the dehydrogenative silylation of dihydrotestosterone using C2-benzyloxy sugar silanes proceeded in 79% yield to provide intermediate **55**. A more sterically hindered carbohydrate acceptor gave **56** in a reduced yield of 57% and was accompanied by a significant formation of homodimer. While theoretically best with secondary alcohols, additional equivalents of sugar silane allow for the use of $B(C_6F_5)$ with primary alcohols as well. The C6 position of a methyl glucoside was silylated to afford **57** in 60% yield when 1.5 equivalents of sugar silane was used. This yield was increased to 78% when 2.7 equivalents of sugar silane was used with 9 mol% catalyst. Due to the ability to glycosylate the mixtures of tethered intermediates and homodimer, it is likely that this strategy can be used with a variety of secondary glycosyl acceptors in addition to secondary glycosyl acceptors.

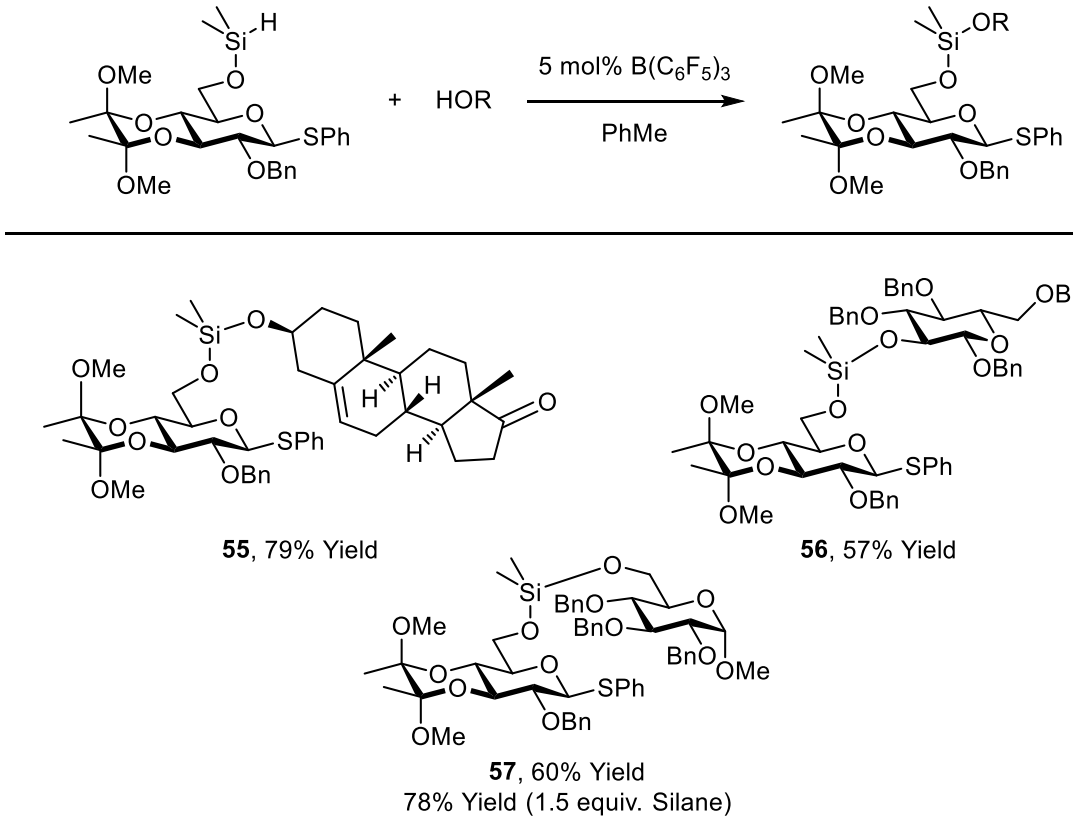
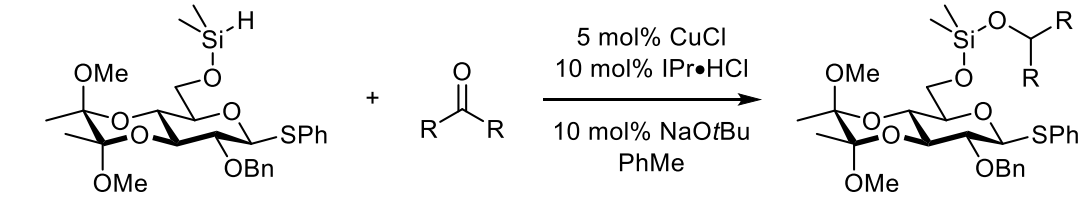
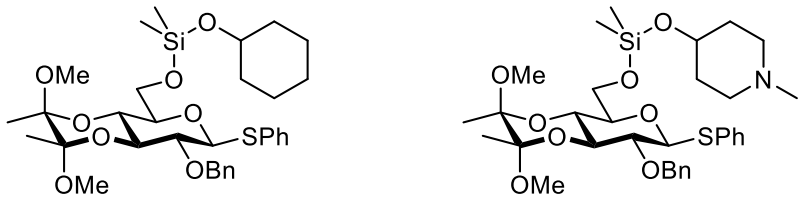


Table 3.13 – Catalyzed Silylations Using C2-Benzyloxy Sugar Silanes

A continuing goal of the sugar silane project is the innovative use of the silicon-hydride functionality to introduce glycosidic bonds from non-traditional glycosyl acceptors. Previous work towards the synthesis of glycosidic bonds from ketones was motivation to explore the use of carbonyl glycosyl acceptors with C6 sugar silanes. The same copper-NHC catalyst used for the dehydrogenative silylation of alcohols has been shown to be competent for the hydrosilylation of ketones. Initial attempts for the hydrosilylation of ketones with C6 sugar silanes focused on the same optimized procedure for the dehydrogenative silylation of alcohols, mainly a 1:2 ratio of copper to NHC. Gratifyingly, 70% of intermediate **50** was obtained from the hydrosilylation of cyclohexanone (Table 3.14). A more highly functionalized aminoketone was shown to

undergo the process in a lower but still useful 54% yield to provide intermediate **58**. While the use of ketones as substrates was not highly explored, these examples show that they are compatible for use with C6 sugar silanes.





50, 70% Yield

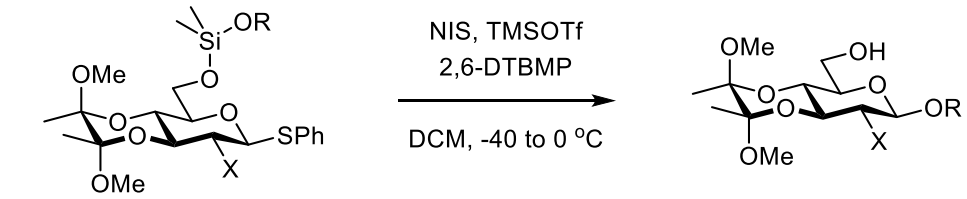
58, 54% Yield

Table 3.14 – Hydrosilylation of Ketones Using Sugar Silanes

Glycosylation of 2-Benzyloxy Sugar Silanes

Intermolecular glycosylations lacking a participating group at the C2 hydroxyl typically result in a mixture of α and β anomeric products. The ability to deliver glycosyl acceptors tethered to the C6 hydroxyl provides a strategy to stereoselectively access β-glucosides without participating protecting groups. Gratifyingly, activation of 2-benzyloxy C6 sugar silanes resulted in high yielding glycosylation reactions without any formation of the α-anomer. In addition to providing total selectivity at the anomeric position, intramolecular glycosylations with 2-benzyloxy sugar silanes also return higher yields than their 2-acetoxy counterparts. Glycoside **59** was obtained in 85% yield, an increase over the 75% yield for **38** (Table 3.15). Cyclohexanol was only glycosylated in 64% yield using 2-acetoxy sugar silanes, however 2-benzyloxy sugar silanes returned β-

glucoside **60** in 92% yield. The improvement in yield is possibly due to a more stable and therefore less reactive oxocarbenium cation as the C2 substituent is altered to the more electron donating benzyloxy group. Succinimide is present in stoichiometric amounts due to the use of NIS and has been shown to be an active nucleophile when more hindered glycosyl acceptors are used for intramolecular glycosylation. It is possible that the more reactive C2-acetoxy sugar silane is hindered by additional succinimide addition.



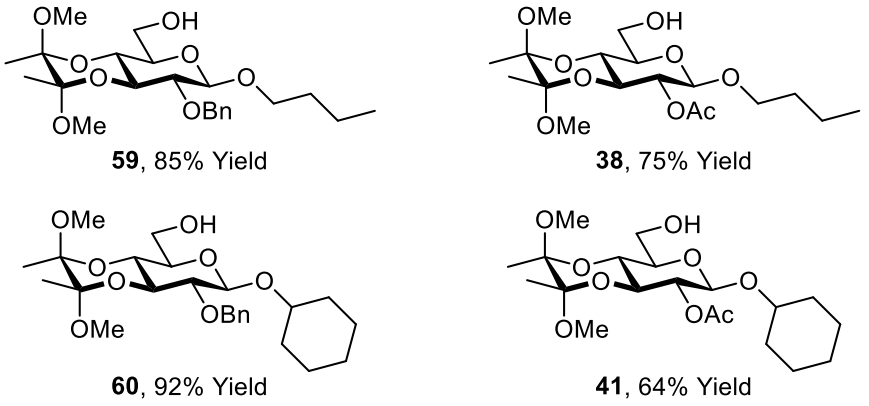
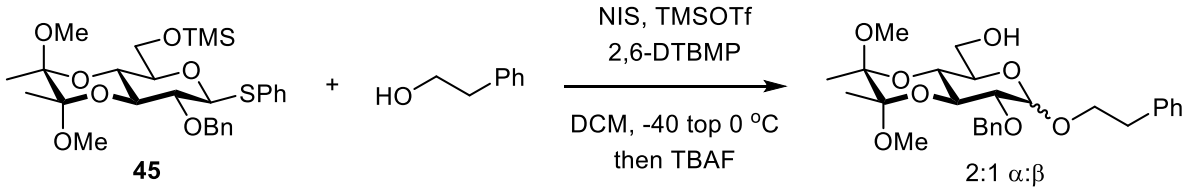


Table 3.15 – Comparison of 2-Benzyloxy and 2-Acetoxy Sugar Silanes

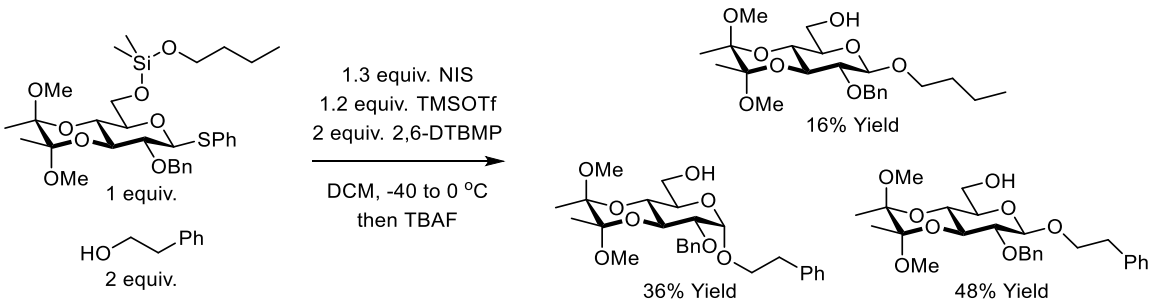
The lack of a participating group at the C2 position in these sugar silanes and the total stereoselectivity of the glycosylations indicate that the reaction is most likely going through an intermolecular mechanism. Considering the amount of research that has gone into the effect of distal protecting groups on the stereoselectivity of intermolecular glycosylations, a control experiment was run to see the effect of the 1,2-*trans* diol protecting group on an intermolecular glycosylation. Thioglycoside **45** was protected

with a trimethylsilyl ether to closely approximate the structure of sugar silanes. The intermolecular glycosylation reaction between this fully protected donor and phenethyl alcohol resulted in a diasteromeric mixture favoring the α-anomer in a two to one ratio (Scheme 3.21). This showed that the stereocontrol is derived from the intramolecular nature of the reaction and that the 1,2-trans-diol protecting group only serves the role of inhibiting formation of the 1,6-anhydro byproduct.



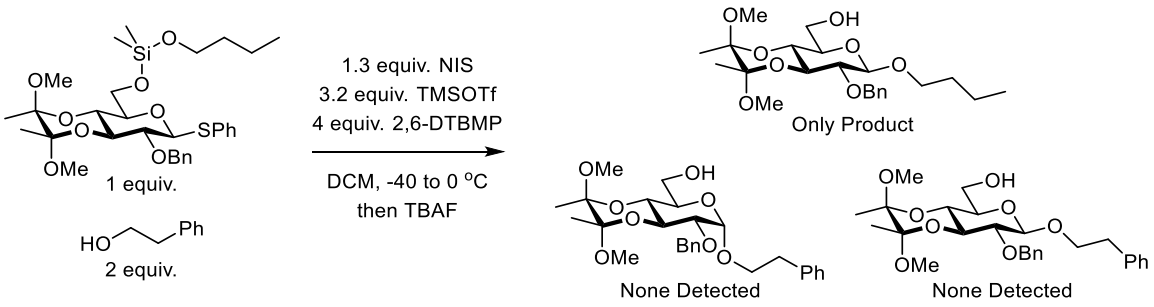
Scheme 3.21 – Intermolecular Control Experiment

The addition of an exogenous alcohol to the intramolecular glycosylation of a sugar silane was also studied (Scheme 3.22). The main point of this reaction was to study the potential performance of a multifunctional nucleophile-bearing glycosyl acceptor. For example, a tethered glycosyl acceptor containing an additional unprotected alcohol could undergo an intermolecular reaction where the undesired nucleophile forms a new glycosidic bond. Unfortunately, the glycosylation with two equivalents of phenethyl alcohol favored the addition of the exogenous alcohol. 36% of the α-anomer and 48% of the β-anomer were recovered from the formation of phenethyl glucoside while only 16% of the intramolecular glycosylation was seen. This showed that the intermolecular glycosylation with a free hydroxyl group is actually faster than the desired intramolecular reaction.



Scheme 3.22 – Exogenous Alcohol Control Experiment with 1.2 equiv. TMSOTf

Fortunately, the use of NIS-TMSOTf as the glycosylation activator provides a route to inhibit the intermolecular glycosylation. Additional equivalents of TMSOTf can be used to silylated any free alcohols in the reaction, essentially adding a protecting group *in situ*. The reaction from Scheme 3.21 was repeated with an additional two equivalents of TMSOTf to account for the exogenous alcohol. Gratifyingly, the reaction proceeded smoothly without any formation of either the α- or β-anomer of phenethyl glucoside; the only material recovered was the desired butyl β-glucoside (Scheme 3.23). While the intermolecular glycosylation is in fact favored, it can be completely inhibited by the use of excess TMSOTf to negate the nucleophilicity of any other alcohols on the glycosyl acceptor.

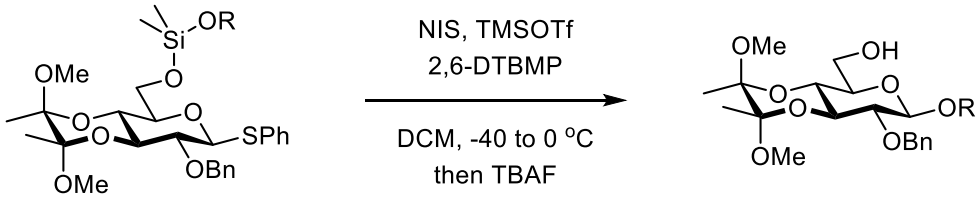


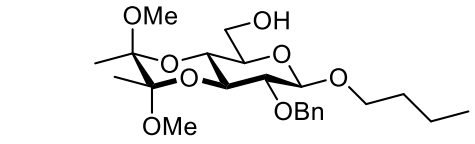
Scheme 3.23 – Exogenous Alcohol Control Experiment with 3.2 equiv. TMSOTf

A variety of alcohols were explored to gauge the scope of the reaction (Table 3.17). As previously discussed, the method is high yielding with primary alcohols. Butanol and phenethyl alcohol were glycosylated efficiently to give the desired β-glycosides **59** and 61 in 85% and 86% yield, respectively. More complex carbohydrate primary alcohols are also tolerated depending on the stereochemistry of the C4 hydroxyl as well as the protecting group scheme used. Disaccharide **62** from a tribenzyl protected methyl glycosyl acceptor was obtained in 74% yield. Galactoside acceptors were also shown to tolerate the method as the tethering and glycosylation to give **63** proceeded in 41% over two steps. While the tethered intermediate requisite to obtaining **63** was not purely isolated, its glycosylation in the presence of homodimer byproduct was similarly efficient to the synthesis of **62**. Unfortunately, an attempt at an iterative glycosylation strategy using C6 delivery encountered lower yields. The glycosylation to afford **64** returned only 36% of the desired glycoside.

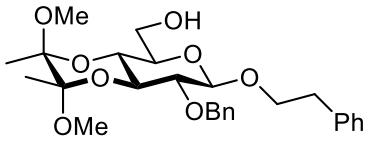
Simple secondary alcohols also tolerate the intramolecular glycosylation. Cyclohexyl β-glucoside **60** was obtained in 92% yield. Like their 2-acetoxy counterparts, 2-benzyloxy sugar silanes struggle to undergo C6 delivery with more sterically hindered glycosyl acceptors. The delivery of menthol resulted in only 32% of glycoside **65**. A significant amount of succinimide addition to the anomeric position was recovered along with some 1,6-anhydro byproduct. The C2 position of benzyl tri-*O*-benzylglucoside was tethered relatively efficiently, however the glycosylation did not proceed and none of glycoside **66** was detected. Puzzlingly, the use of a hydroxylamine shut down the reaction as well. While C2 sugar silanes had been shown to deliver good yields of the corresponding glycosides, multiple attempts to obtain **67** through C6 delivery failed.

Interestingly, it appears that the lack of reactivity was a result of little of the glycosyl donor being activated.

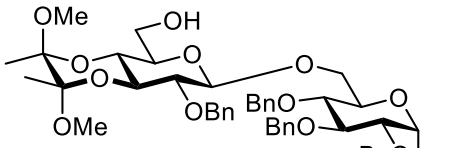




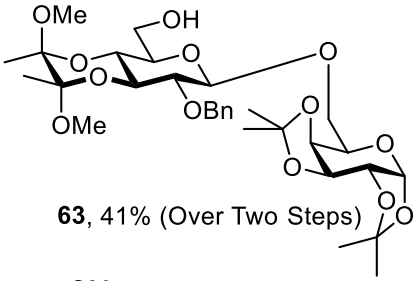
59, 85% Yield



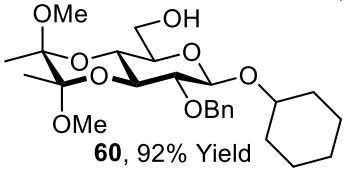
61, 86% Yield



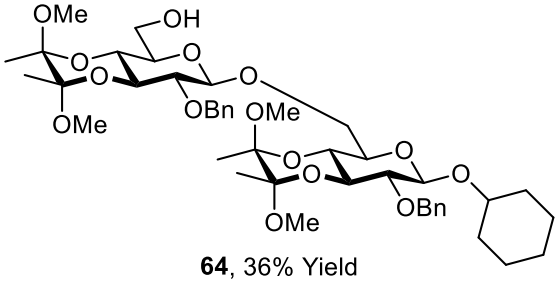
62, 74% Yield



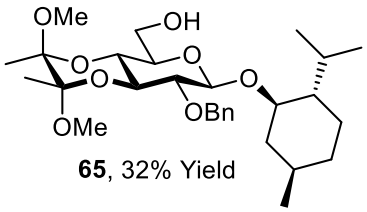
63, 41% (Over Two Steps)



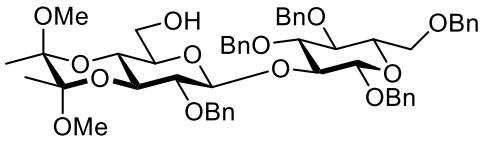
60, 92% Yield



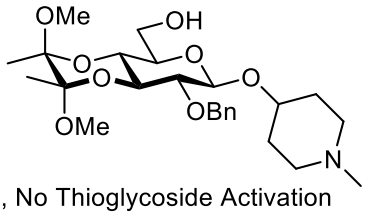
64, 36% Yield



65, 32% Yield



66, No Desired Product



67, No Thioglycoside Activation

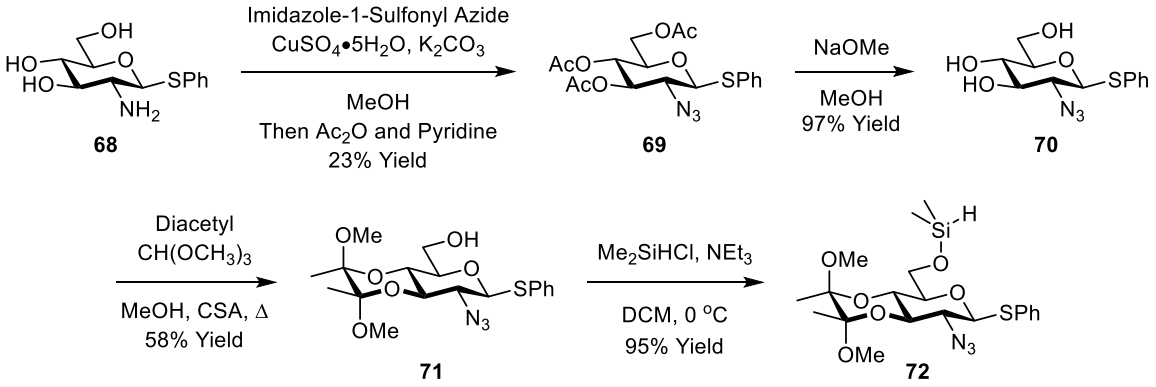
Table 3.16 – Substrate Scope with 2-Benzyloxy Sugar Silanes

2-Azido Sugar Silanes

The ability to successfully obtain β-glucosides through intramolecular aglycone delivery using C2-benzyloxy sugar silanes indicated that other common C2 substituents that do not participate in the oxocarbenium could be competent glycosyl donors. The azido group is often installed at the C2 position of a glycosyl donor to act as a protecting group for the amine functionality of glycosamines. The inability to participate in the reaction mechanism makes 2-azido-β-glucosides particularly difficult to synthesize.

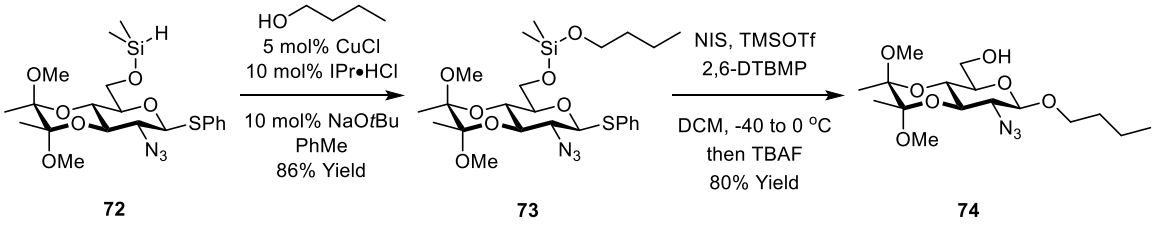
While 2-azido-thioglycosides have been previously reported, they have only been synthesized as a mixture of diastereomers at the anomeric position. Trifluoromethanesulfonyl azide was developed as a reagent to convert amines to azides, however the reagent is explosive and is not stable for long-term storage. Alternatives to trifluoromethanesulfonyl azide, such as imidazole-1-sulfonyl azide, have been designed to overcome these challenge and improve the safety of azide installation.[100] The commercial availability of imidazole-1-sulfonyl azide allowed a new route to 2-azido-thioglycosides by starting with the known thioglucosamine **68** and provides it in diastereomerically pure form (Scheme 3.24). Thioglucosamine **68** was treated with imidazole-1-sulfonyl azide and potassium carbonate in the presence of catalytic copper (I) sulfate. While unnecessary for this synthesis, the published procedure then acetylates any free hydroxyls to ease purification. Following the published procedure as closely as possible, the compound was converted to triacetylated **69** which was recovered in only 23% yield. While low yielding, the reaction provided enough material to continue the synthesis and test the compatibility of 2-azido thioglycosides as sugar silanes. Acetylated **69** was then exposed to catalytic sodium methoxide to give deprotected **70** in 97% yield.

The treatment of **70** with conditions to generate the 1,2-*trans* diol protecting group gave **71** in 58% yield. Finally, **71** was converted to 2-azido sugar silane **72** in 95% yield upon exposure to the general procedure.



Scheme 3.24 – Synthesis of 2-Azido Sugar Silanes

With the 2-azido C6 sugar silane in hand, it was subjected to the general procedure developed for the dehydrogenative silylation of alcohols. The silylation was efficient and intermediate **75** was obtained in 86% yield (Scheme 3.25). Upon exposure to activating conditions, **75** was converted to 2-azido-β-glycoside **76** in 76% yield. While no control reactions were performed, the high degree of stereoselectivity indicates that the reaction is most likely proceeding through an intramolecular delivery mechanism. Due to the similar mechanism, 2-azido sugar silanes will likely have similar reactivity as the 2-benzyloxy sugar silanes: suitable for primary and simple secondary alcohols, but likely encountering decreased yields as the steric complexity proximal to the alcohol is increased.



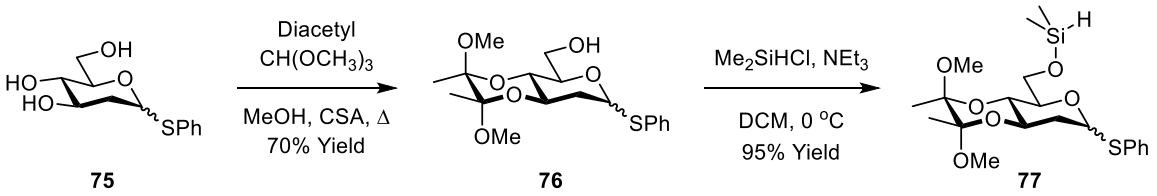
Scheme 3.25 – 2-Azido Sugar Silane Tethering and Glycosylation

3.5) 2-Deoxy Sugar Silanes

2-Deoxy-β-glycosides can be particularly difficult to synthesize due to the lack of a directing group at the C2 position.[62,101] Furthermore, the anomeric effect tends to favor the formation of the α-anomer. In addition to the previous examples using 2-acyloxy, 2-benzyloxy, and 2-azido sugar silanes, we envisioned the use of C6 delivery to be a valuable tool to provide stereocontrol in the synthesis of 2-deoxy-β-glycosides.

Synthesis of 2-Deoxy Glycosides

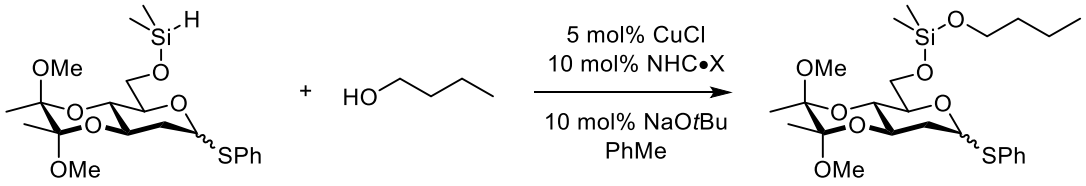
The synthesis of 2-deoxy sugar silanes was straightforward from known 2-deoxy-thioglycoside **75**, however installation of the thiol leaving group resulted in a diastereomeric mixture due to the lack of a substituent at the C2 position (Scheme 3.26). While the stereochemistry of the anomeric position could potentially influence the subsequent glycosylation, the directing effect of C6 delivery and likelihood of an S_N1-like mechanism appear to remove any effects of the glycosyl donor anomeric mixture. The only impact of the mixture was the increased complexity of spectroscopic data. The exposure of **75** to conditions for 1,2-*trans* diol generation gives protected **76** in 70% yield. As usual, the protection of the C6 hydroxyl with a dimethyl silyl-ether proceeded efficiently and gave **77** in 95% yield.



Scheme 3.26 – Synthesis of 2-Deoxy Glycosides

Silylation of 2-Deoxy Glycosides

The dehydrogenative silylation of alcohols with 2-deoxy sugar silanes is efficient using the previously optimized procedure (Table 3.17). The dehydrogenative silylation of butanol with 2-deoxy sugar silane proceeded in 88% yield. Previous reports from Nolan indicated that SIMes•HBF_4 and ICy•HBF_4 were also very good ligands for the hydrosilylation of ketones,[96,97] however their use for the dehydrogenative silylation of alcohols at a 1:2 CuCl:NHC•X ratio returned very little of the desired product. Therefore, IPr•HCl was continued as the ligand of choice.

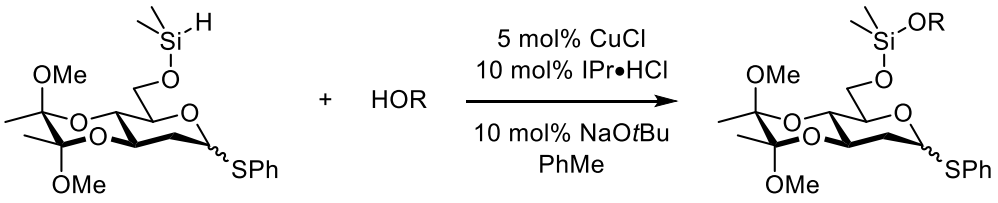


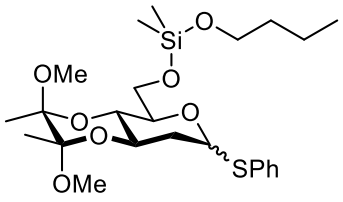
NHC•X	Yield
IPr•HCl	88%
SIMes•HBF_4	Decomposition
ICy•HBF_4	Decomposition

Table 3.17 – Exploration of Alternative Ligands

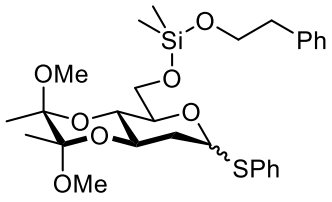
A variety of alcohols were silylated using the optimized procedure (Table 3.18). As previously mentioned, the silylation of butanol with 2-deoxy sugar silane proceeded

in 88% yield to give **78**. Another primary alcohol, phenethyl alcohol, provided 2-deoxy-β-glycoside **79** in a similar 87% yield. As the steric bulk of the alcohol increased, there was a noticeable drop off in yield and their dehydrogenative silylation with 2-deoxy sugar silanes was typically less efficient than previous sugar silanes. The reduction in yield could be countered with the use of additional sugar silane and tethered intermediates made from simple alcohols were typically easily purified. The silylation of isobutanol to provide **80** was boosted to near quantitative yield by using 1.5 equivalents of sugar silane. Unfortunately, cyclohexylmethanol was silylated to afford **81** in only 57% yield despite the use of additional sugar silane. Secondary alcohols were lower yielding than primary alcohols. Isopropanol and cyclohexanol were silylated in yields of 56% and 72% to give **82** and **83**, respectively. The silylation of cyclohexanol could be boosted to 85% yield using 1.5 equivalents of sugar silane. Finally, menthol was silylated to provide **84** using 1.1 equivalents of sugar silane in 67% yield.

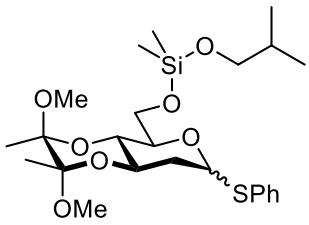




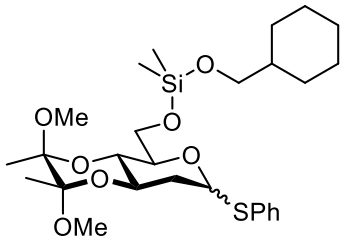
78, 88% Yield



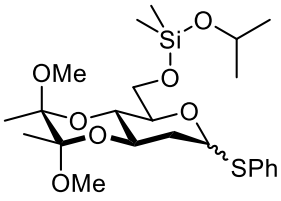
79, 87% Yield



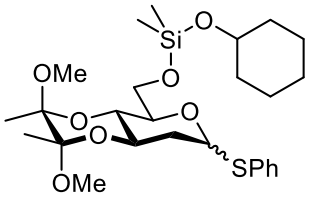
80, 99% Yield (1.5 equiv. silane)



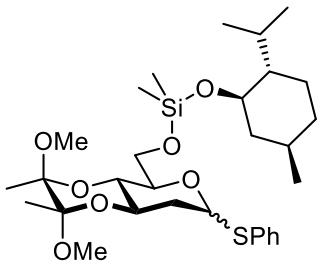
81, 57% Yield (1.5 equiv. silane)



82, 56% Yield



83, 72% Yield
85% Yield (1.5 equiv silane)

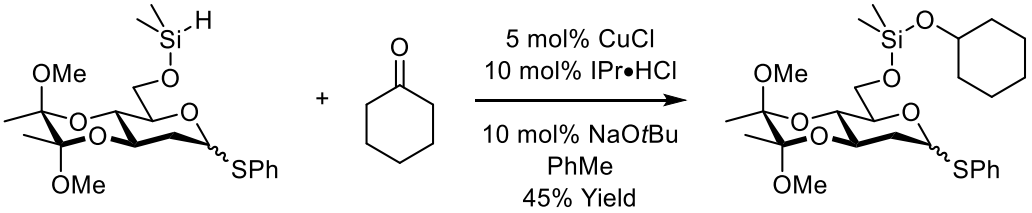


84, 67% Yield

Table 3.18 – Scope of Alcohol Silylation Using 2-Deoxy Sugar Silanes

The dehydrogenative silylation of alcohols using 2-deoxy sugar silanes are often lower yielding than with the previously described sugar silanes. The lower yields are possibly due to an impurity from their synthesis. Carbohydrates are notoriously difficult to crystallize and at no point during the synthesis of 2-deoxy sugar silanes was any recrystallization possible; flash chromatography was the only purification method used. Many of the steps for the synthesis of these sugar silanes resulted in a number of byproducts and the desired product was often a diastereomeric mixture. Despite the sugar silanes being spectroscopically pure via ^{1}H and ^{13}C NMR, it is possible that an impurity was carried forward in the synthesis. Fortunately, the lower yields can be somewhat offset by the use of additional silane. While this is accompanied by additional homo-dimer byproduct formation, the homodimer can either be removed or the tethered intermediate glycosylated in its presence.

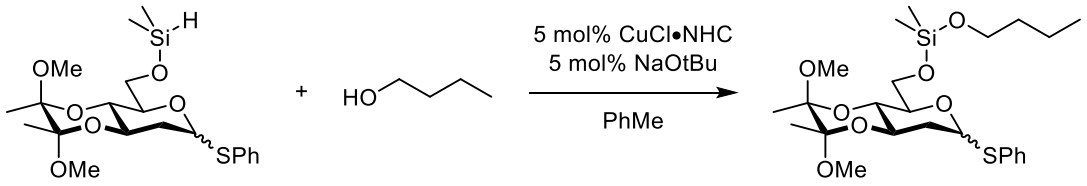
In addition to the dehydrogenative silylation of alcohols, the hydrosilylation of ketones with 2-deoxy sugar silanes is particularly interesting. In this example, an unusual glycosyl acceptor is utilized for the generation of a particularly difficult glycosidic bond. While the hydrosilylation of cyclohaxanone proceeded in only 45% yield, it is still a valuable transformation due to its unusual nature (Scheme 3.27). Furthermore, the yield of the hydrosilylation can likely be improved with the use of additional sugar silane.



Scheme 3.27 – Hydrosilylation of Cyclohexanone with 2-Deoxy Sugar Silanes

All of the dehydrogenative silylations and hydrosilylations up to this point had been catalyzed by a copper-NHC catalyst formed *in situ* from copper (I) chloride and NHC salts. However, discrete copper-NHC catalyst have been reported by Nolan to have even better reactivity than their *in situ* analogs. The commercial availability and improved reactivity of these discrete catalysts make them an attractive alternative. Furthermore, the potential for base-catalyzed decomposition of the sugar silane is reduced due to the catalyst requiring only half as much of NaOtBu as compared to the *in situ* prepared catalyst.

Two discrete catalysts, CuCl•IMes and CuCl•IPr, were explored for their ability to catalyze dehydrogenative silylations with 2-deoxy sugar silanes (Table 3.19). In accordance with previous results, CuCl•IMes performed poorly in the reaction and only 26% of the tethered intermediate was obtained. While IMes is a suitable ligand for reactions involving C2 sugar silanes, the more sterically hindered IPr has continually proven to be a much better ligand with C6 sugar silanes. Indeed, the discrete CuCl•IPr promoted the dehydrogenative silylation of butanol with 2-deoxy sugar silane in 74% yield. A significant amount of silanol was detected during the reaction. To prevent this byproduct, the reaction was run with molecular sieves and the yield improved to 88%, roughly the same efficiency as with the *in situ* catalyst. The yield was even further improved to 97% with the use of 1.5 equivalents of sugar silane.



Catalyst	Conditions	Yield
CuCl•IMes	1.1 equiv. silane	26%
CuCl•IPr	1.1 equiv. silane	74%
CuCl•IPr	1.1 equiv silane molecular sieves	88%
CuCl•IPr	1.5 equiv. silane molecular sieves	97%

Table 3.19 – Discrete CuCl•NHC Catalysts

A variety of alcohols were tested with the discrete catalyst (Table 3.20). As previously mentioned, the dehydrogenative silylation of butanol proceeded in 88% yield to give **78**. Secondary alcohols gave reduced but still synthetically useful. Isopropanol was silylated and afforded 64% of the tethered intermediate **82**. The reaction with cyclohexanol also proceeded efficiently and provided **81** in 70% yield. While the *in situ* catalyst is slightly more efficient with primary alcohols, the discrete catalyst is better with secondary alcohols.

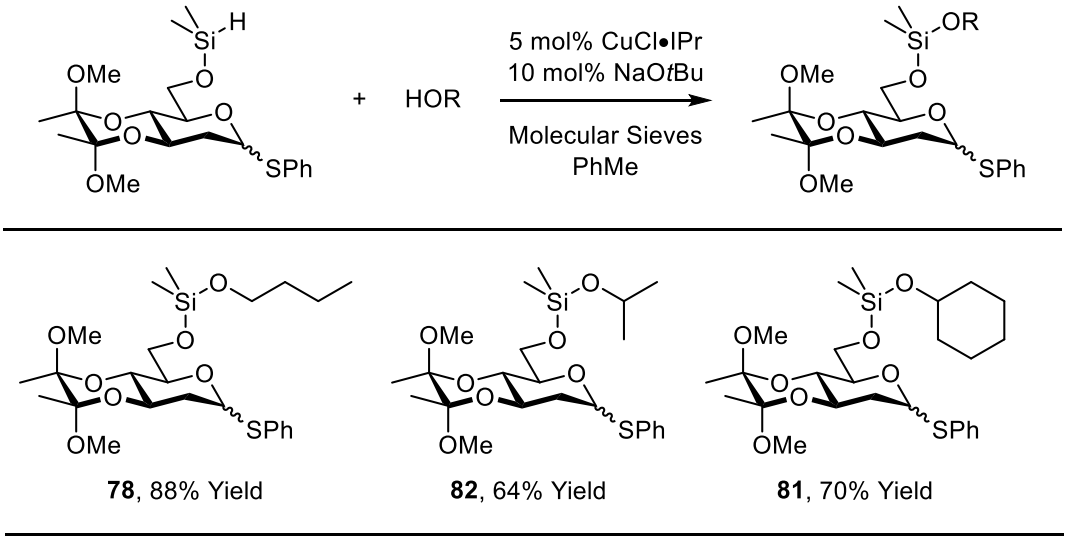
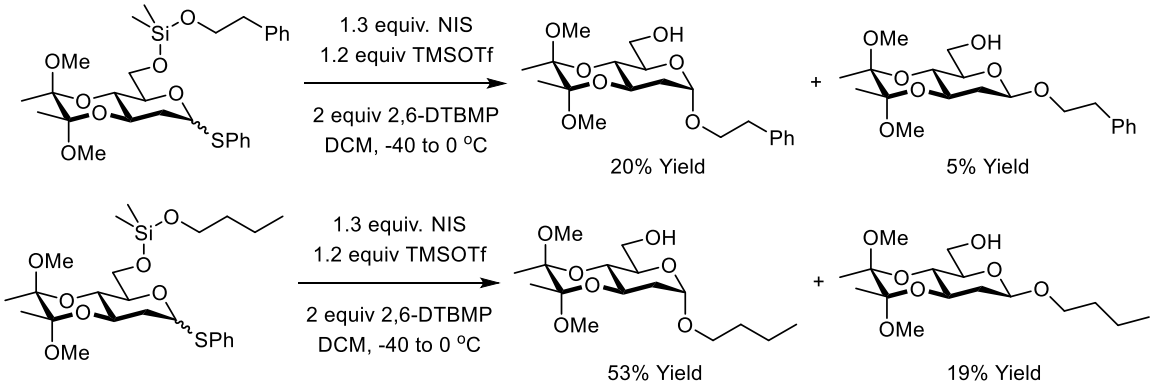


Table 3.20 – Scope of Alcohol Dehydrogenative Silylation with Discrete Catalyst

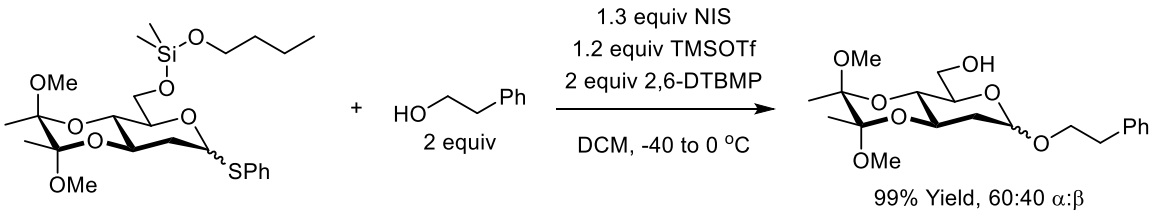
Glycosylation of 2-Deoxy Sugar Silanes

Having gained access to the requisite tethered intermediates, attention was turned towards the glycosylation of 2-deoxy sugar silane. Surprisingly, a first attempt with phenethyl alcohol was low yielding and favored the formation of the α-anomer (Scheme 3.28). This marked the first time that the formation of an α-anomer was seen using C6 delivery. The delivery with butanol was higher yielding, yet again the α-anomer was the favored product.



Scheme 3.28 – Initial Glycosylations of 2-Deoxy Sugar Silanes

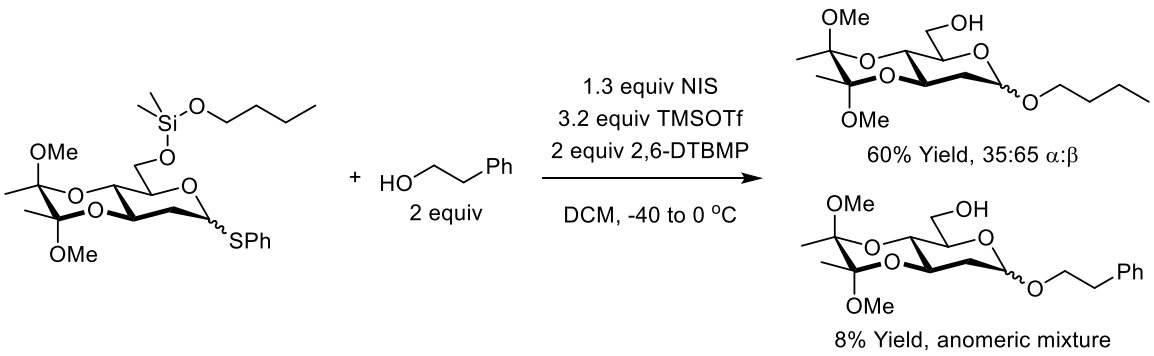
Initial thinking was that there may be something about 2-deoxy sugar silanes which favors an intermolecular delivery over an intramolecular delivery. A particularly slow intramolecular reaction could be impeded by the formation of intermolecular products. An obvious experiment to test the intermolecularity of the glycosylation is to perform a glycosylation in the presence of an exogenous alcohol. The glycosylation of butanol tethered intermediate **80** in the presence of two equivalents of phenethyl alcohol using 1.2 equivalents of TMSOTf gave an almost quantitative yield of the phenethyl glycoside resulting from exogenous addition (Scheme 3.29). The reaction favored the formation of the α-glycoside in a 60:40 ration. The near quantitative yield of the intermolecular product indicates that the intramolecular glycosylation is much slower than the intermolecular reaction of a free alcohol.



Scheme 3.29 – Glycosylation with Unprotected Exogenous Alcohol

Since an anomeric mixture results from the glycosylation of aglycones tethered to 2-deoxy sugar silanes, a better control experiments would involve additional TMSOTf to protect the exogenous alcohol as a silyl ether. As the silyl ether, the exogenous alcohol should more closely resemble the nucleophilicity of the tethered glycosyl acceptor for an intermolecular reaction. Upon reaction with 3.2 equivalents of TMSOTf, the intermolecular glycosylation with exogenous alcohol was greatly reduced (Scheme 3.30). Only an 8% yield of the phenethyl glycoside was obtained as an anomeric mixture. The

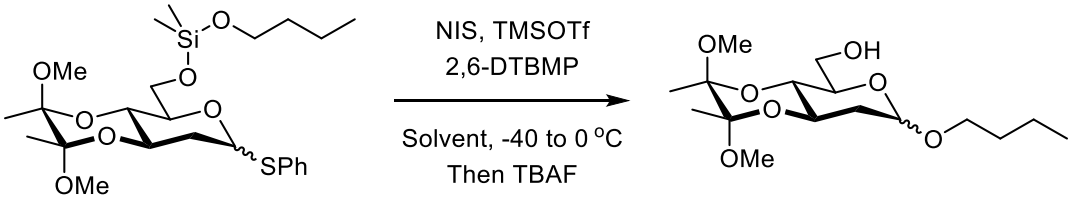
main product of the reaction was the butyl glycoside resulting from either inter- or intramolecular glycosylation with the tethered glycosyl acceptor. A reversal of selectivity was seen in this control reaction, as the β-anomer was now favored in a 2:1 ratio. This indicates that some intermolecular glycosylation is taking place to overcome the influence of the anomeric effect which should favor the α-anomer. The addition of succinimide was also detected, indicating a relatively slow process overall.



Scheme 3.30 – Control Reaction with Additional TMSOTf

The solvent used in a glycosylation reaction can have a drastic effect on the stereoselectivity of the newly formed glycoside. This is due to the solvent-stabilizing effect on oxocarbenium ions generated during the reaction. The linear acetonitrile has been shown to interact with the axial face of an oxocarbenium due to the preference of the anomeric effect. Incoming glycosyl acceptors are encouraged to approach the glycosyl donor to form β-glycosides due to this interaction. Alternatively, the more sterically encumbered tetrahydrofuran interacts with the equatorial face and incoming acceptors are more likely to form α-glycosides. Due to the unexpected formation of anomeric mixtures when attempting to deliver glycosyl acceptors intramolecularly from the C6 position, the effect of these co-solvents in the glycosylation was explored (Table 3.21). A 1:1 solvent mixture of methylene chloride and tetrahydrofuran returned a lower

yield and showed similar diastereoselectivity as with methylene chloride alone. Alternatively, no glycosyl donor activation was seen when acetonitrile was used as a cosolvent. This was most likely due to solubility issues with NIS.

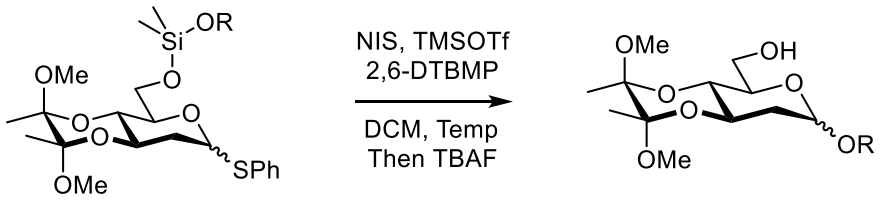


Solvent	Yield	Selectivity
DCM	72%	73:27 α:β
1:1 DCM:THF	55%	75:25 α:β
1:1 DCM:MeCN	No Reaction	N/A

Table 3.21 – Effect of Solvent on 2-Deoxy Sugar Silane Glycosylations

Suspicion of an intermolecular mechanism as the cause for anomerization led to the exploration of temperature effects on the glycosylation. Up to this point, all glycosylations had been attempted by adding TMSOTf to a reaction stirred at -40 °C. After five to ten minutes, the reaction was gently warmed to 0 °C until no starting material remained and was then quenched. The previously optimized procedure resulted in a 72% yield of an anomeric mixture favoring the α-glycoside in a 73:27 ratio. Warming the reaction to room temperature instead of 0 °C gave a similar yield of 71%, however the stereoselectivity was reversed and the β-glycoside was now favored in a 78:22 ratio (Table 3.22). Keeping the temperature at -40 °C for the entire reaction saw a slight reduction in the yield to 62%, however again the β-anomer was preferred in a 60:40 ration. While the temperature clearly has an effect on the diastereoselectivity of the

glycosylation, no clear trends could be drawn since both an increase as well as a decrease in temperature favored the β-anomer. Gratifyingly, the further reduction of temperature to -78 °C afforded the β-glycoside in 75% yield without any sign of the α-anomer. This result was repeatable and proved to be applicable to secondary alcohols as well, albeit at a lower yield. The glycosylation of cyclohexanol resulted in a 38% yield of the β-glycoside whereas higher temperatures return a lower yielding anomeric mixture.

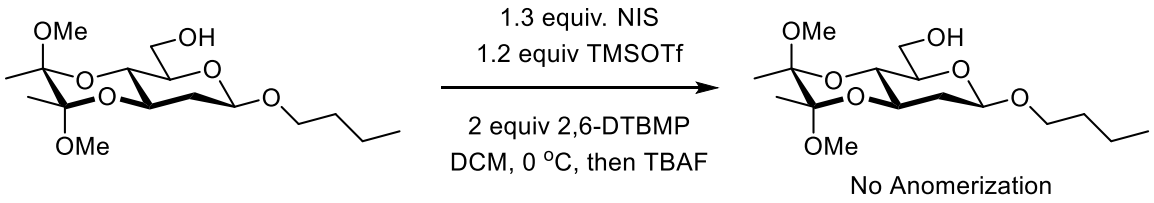


Acceptor	Temperature	Yield	Stereoselectivity
HO	-40 °C to rt	71%	22:78 α:β
HO	-40 to 0 °C	72%	73:27 α:β
HO	-40 °C	62%	40:60 α:β
HO	-78 °C	75%	β only
HO	-40 to 0 °C	24%	65:35 α:β
HO	-78 °C	38%	β only

Table 3.22 – Effect of Temperature on 2-Deoxy Sugar Silane Glycosylations

Without any obvious trend for the lack of stereoselectivity at warmer temperatures, it is possible that the reaction is proceeding through an intramolecular mechanism. Anomerization could take place under the reaction conditions at warmer temperatures but not at cooler temperatures. With newly acquired access to 2-deoxy β-glycosides, butyl 2-deoxy-glycoside was resubjected to the reaction conditions at a warm

enough temperature that anomerization could be expected to take place (Scheme 3.31). Upon workup and isolation, the material was recovered almost quantitatively without any sign of the α-anomer.



Scheme 3.31 – Product Resubjected to Reaction Conditions

While Scheme 3.31 depicts the resubjection of the β-glycoside to the reaction conditions, it is actually somewhat difficult to completely recreate the conditions of the reaction. Presumably, upon delivery of the glycosyl acceptor to the anomeric center, an electron deficient silicon remains tethered to the C6 hydroxyl. The acid-catalyzed mutarotation of reducing sugars has for many years been known to go through a mechanism where the sugar tautamerizes between its cyclic and acyclic forms (Figure 3.1). We envisioned a scenario where, upon delivery of the glycosyl acceptor, the electron deficient silane could interact with the pyran oxygen to form a new five-membered ring and open the ring to its acyclic form. The C1-C2 bond would then be free to rotate before the collapse back to the pyran form, explaining the formation of both anomers. Trapping of the electron deficient silicon with advantageous water or succinimide would then end the anomerization, followed by TBAF-induced cleavage of the silyl ether.

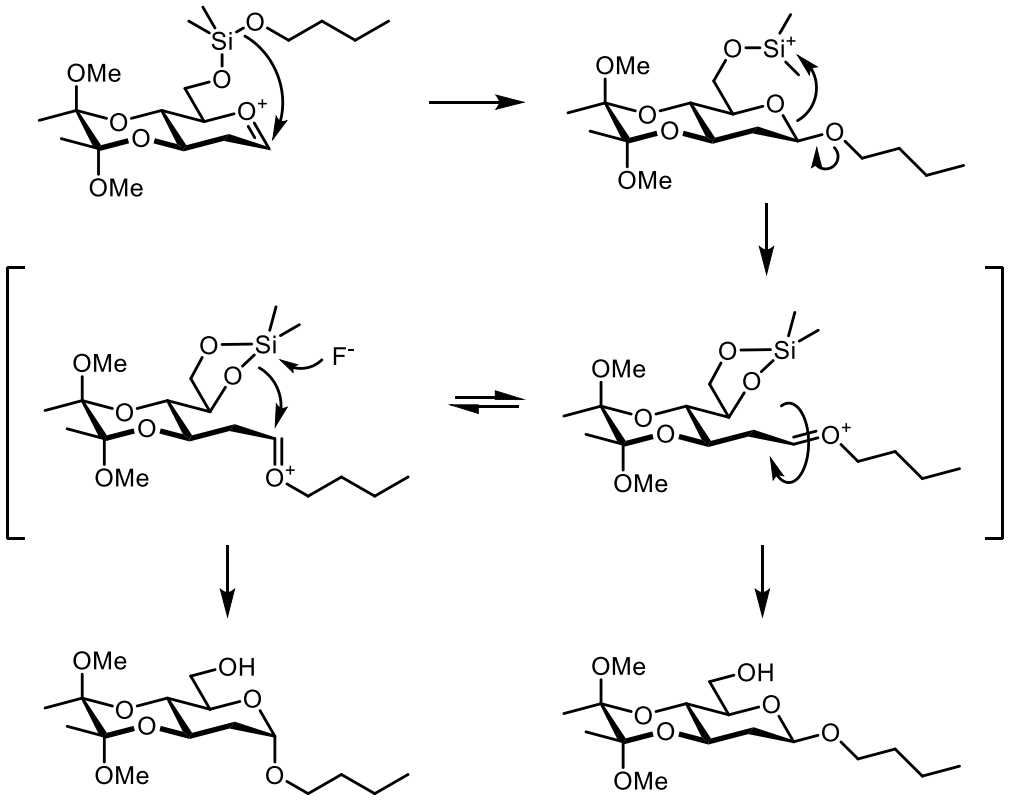
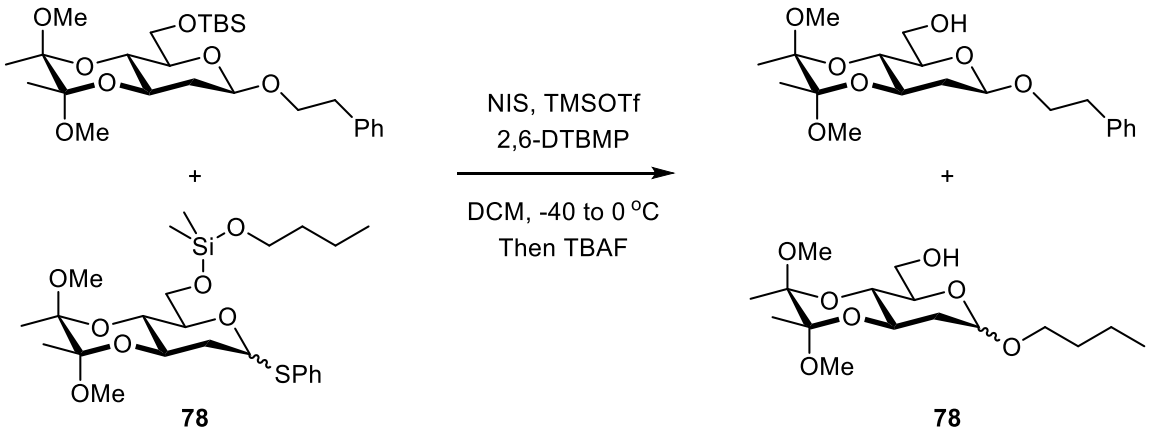


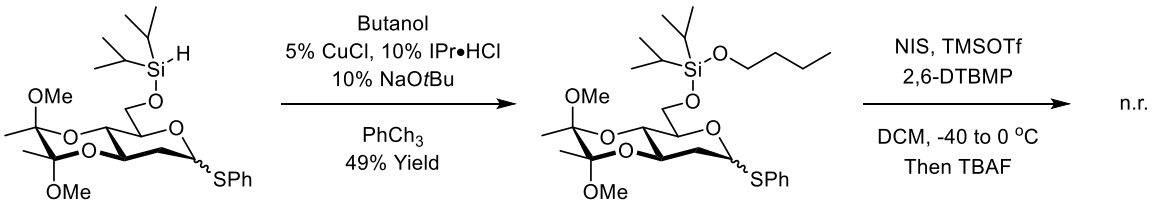
Figure 3.1 – Potential Intramolecular Anomerization Mechanism

Attempts to regenerate a silyl cation through hydride abstraction proved futile, however an intermolecular interaction to promote the intramolecular anomerization was successfully probed. The previously synthesized phenethyl 2-deoxy-β-glycoside was added to tethered intermediate **78**. This mixture was treated with NIS-TMSOTf at a temperature where anomerization typically takes place (Scheme 3.32). If the electron deficient silicon was interacting with an additional pyran ring intermolecularly, the anomerization of phenethyl 2-deoxy-β-glycoside would be expected to take place; however, this product was recovered without any sign of anomerization. This indicates that if the anomerization is derived from the electron deficient silicon, it is most likely proceeding through an intramolecular mechanism.



Scheme 3.32 – Intermolecular Control Reaction

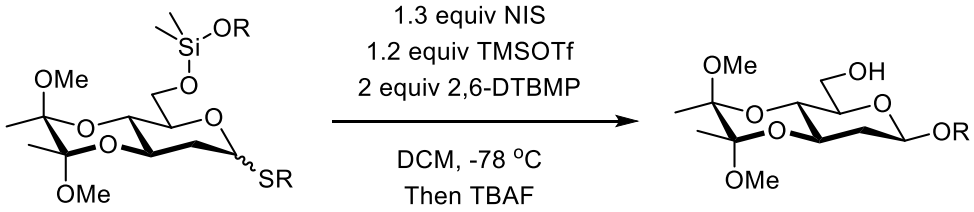
An additional challenge with the glycosylation of 2-deoxy sugar silanes was the reduced yields encountered with secondary glycosyl acceptors. With easy access to diisopropyl sugar silanes, it was worth the time to explore their suitability with 2-deoxy intramolecularly delivery. The dehydrogenative silylation of butanol was achieved in a moderate yield of 49% to access the butanol tethered intermediate (Scheme 3.33). However, despite efficient activation of the thioglycoside, no intramolecular delivery was detected. Instead, only the addition of succinimide was obtained in appreciable amounts.



Scheme 3.33 – Diisopropyl 2-Deoxy Sugar Silanes

The leaving group used on a glycosyl donor can sometimes have a significant effect on the resulting glycosylation. Previous work with C2 sugar silanes showed that, in addition to thiophenyl leaving groups, thioethyl leaving groups are also compatible with

sugar silanes. The requisite sugar silane was synthesized with the same strategy used to access thiophenyl thioglycosides; however, the different leaving group had little effect on the glycosylation (Table 3.23). With both primary and secondary alcohols, the yields were similar.



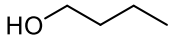
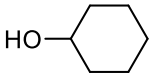
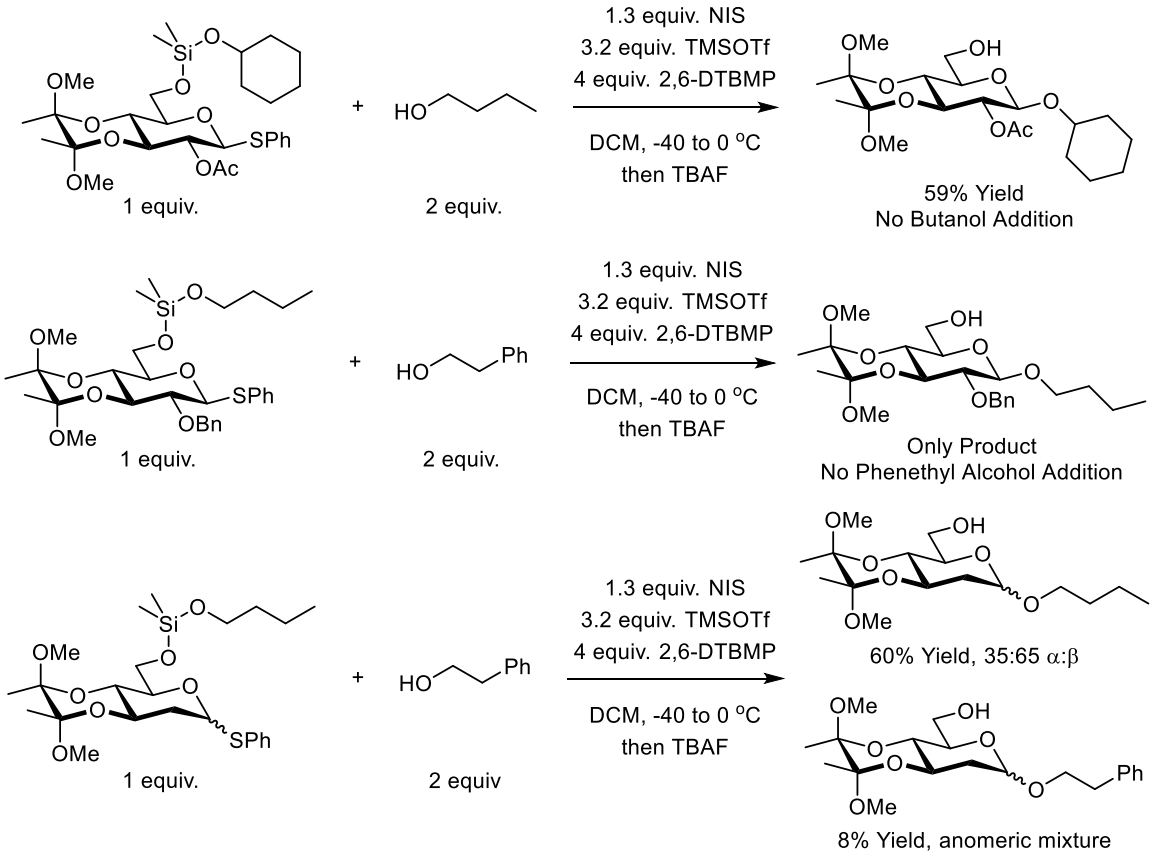
Alcohol	-SPh	-SEt
	88%	89%
	38%	35%

Table 3.23 – Comparison of Leaving Groups

The most likely cause for the erosion of stereochemistry with 2-deoxy sugar silanes is a slower intramolecular delivery. A comparison of control reactions indicates that the intramolecular delivery of aglycones from the C6 position is slower with 2-deoxy glycosyl donors compared to donors with 2-acetoxy and 2-benzyloxy groups (Scheme 3.34). When 3.2 equivalents of TMSOTf is used, there is no evidence of exogenous alcohol addition in the cases with 2-acetoxy and 2-benzyloxy sugar silanes. However, the same experiment with 2-deoxy sugar silanes resulted in an 8% yield of the intermolecular product. Furthermore, an improvement in the diastereoselectivity of the desired product was seen and indicates that some intramolecular delivery is occurring. The formation of α-glycoside is likely due to a competing intermolecular glycosylation. Since the reaction

is likely under kinetic control, the formation of the intermolecular product would be inhibited by decreasing the temperature of the reaction.

Additionally, if an intramolecular anomerization process is taking place due to a silyl cation promoted pyran ring opening, it is most likely not promoted by the intermolecular interaction of a silyl cation. No anomerization of a preformed β-glycoside took place when an additional 2-deoxy glycosylation was performed. Furthermore, it is more difficult to make a case that the intramolecular ring opening would be reduced through decreasing the reaction temperature. It is therefore most likely that the decrease in temperature improves the selectivity by decreasing the rate of intermolecular glycosylation such that it is unable to compete with the intramolecular process.



Scheme 3.34 – Comparison of Control Reactions

As noted, primary alcohols give the desired β-glycosides in good yield. Butyl glycoside **85** was obtained in 88% yield, similar to the same reaction using C2-acetoxy sugar silanes (Table 3.24). Phenethyl glycoside was also glycosylated to provide **86** in 85% yield. was also obtained in good yield. Other primary alcohols were acceptable in the reaction. The silylation of isobutyl alcohol afforded β-glycoside **87** in a modest 66% yield, however cyclohexylmethanol underwent the glycosylation to give **88** in a very efficient 95% yield. There was a relatively steep reduction in yield as the steric bulk of the glycosyl acceptor was increased. While the reactions were still very stereoselective, the additional steric encumbrance of the reaction seems to slow it down to the point that other processes may be favored. Regardless, isopropanol was glycosylated to provide **89** in a 35% yield with total stereoselectivity at the anomeric position. A further reduction in yield to 25% was encountered with cyclohexanol as the glycosyl acceptor to give **91**.

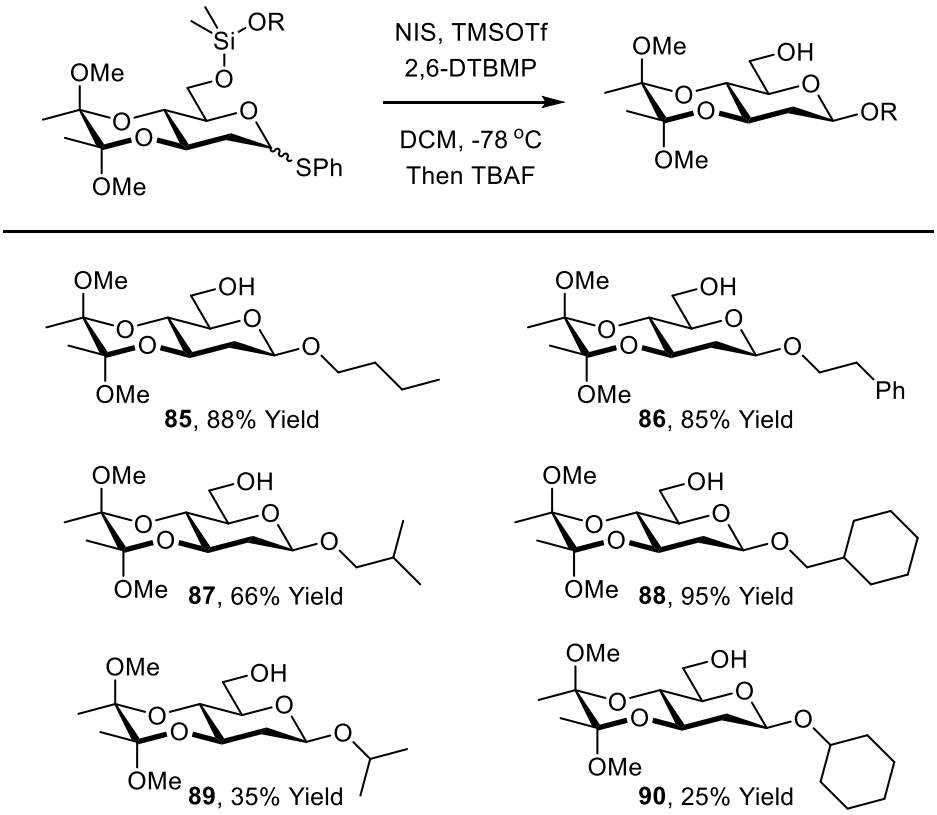
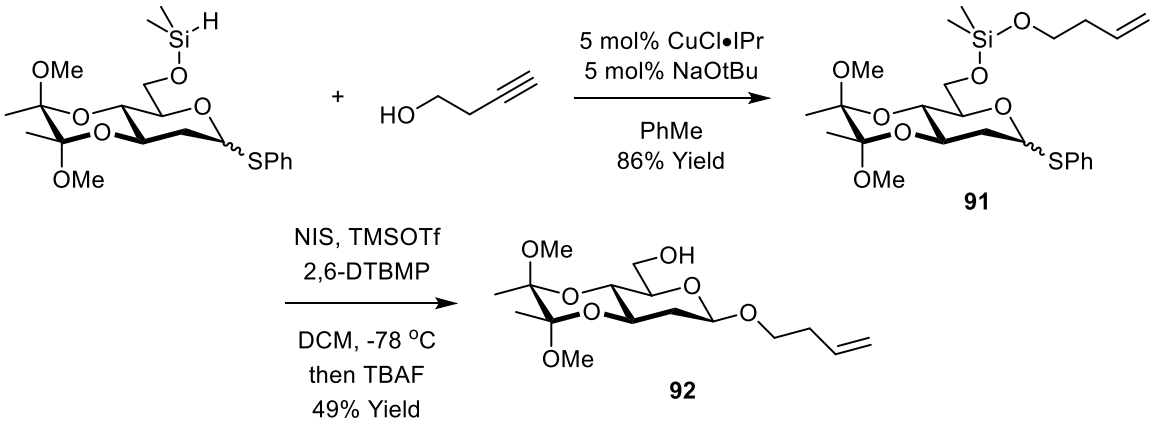


Table 3.24 – Scope of Glycosylations Using 2-Deoxy Sugar Silanes

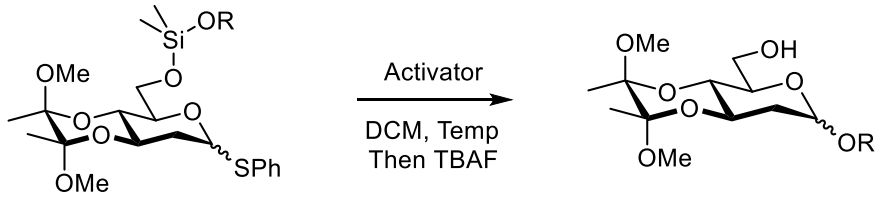
One interesting example that highlights the nuances of working with organometallic catalysts is the use of homopropargylic alcohol as the glycosyl acceptor (Scheme 3.35). Upon subjection to dehydrogenative silylation conditions, the tethered intermediate was recovered in good yield; however, in addition to the silylation of the alcohol, the terminal alkyne had been reduced to the terminal olefin. Glycosylation of this intermediate **93** afforded the resulting β-glycoside in 49% yield.



Scheme 3.35 – Reduction and Glycosylation of Homopropargylic Alcohol

In an attempt to overcome the poor yields with secondary alcohols, additional glycosylation promoters were explored (Table 3.25). As an alternative to stoichiometric amounts of TMSOTf, catalytic triflic acid has been developed to facilitate the N-iodosuccimide promoted activation of thioglycosides. Unfortunately, this promoter resulted in only 33% of the desired product as an anomeric mixture. The lower yields are likely due to acid-catalyzed decomposition of the silyl-tether. DMTST, formed in situ from dimethyl disulfide and methyl triflate, is another activator that has shown limited success with C2 sugar silanes. Its use with butanol as the glycosyl acceptor at -40 °C resulted in a modest 59% yield and an anomeric ratio of 28:72 α:β. Cooling the reaction further to -78 °C decreased the yield to 48%. Improved stereoselectivity was observed, however it was not totally selective and an α:β ratio of 4:96 was obtained. The use of this procedure was explored with secondary alcohols. The glycosylation with isopropanol improved from 35% to 47% with total diastereoselectivity. Unfortunately, cyclohexanol experienced a decrease in yield with poor diastereoselectivity. Finally, methyl triflate

alone was tried as an activator, however decomposition of the tethered intermediate took place and no β-glycoside was obtained.



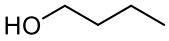
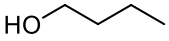
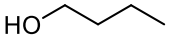
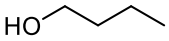
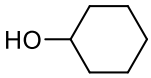
Acceptor	Conditions	Yield	Stereoselectivity
	1.3 equiv NIS 5 mol% TfOH 0 °C	33%	56:44 α:β
	1 equiv. DMTST 2 equiv. 2,6-DTBMP -40 °C	59%	28:72 α:β
	2 equiv. DMTST 2 equiv. 2,6-DTBMP -78 °C	48%	4:96 α:β
	2 equiv. MeOTf -78 °C	Decomposition	N/A
	2 equiv. DMTST 2 equiv. 2,6-DTBMP -78 °C	47%	β only
	2 equiv. DMTST 2 equiv. 2,6-DTBMP -78 °C	21%	24:76 α:β

Table 3.25 – Alternative Glycosylation Activators

Conclusion

The results discussed in chapter three describe advancements in the range of products accessible using sugar silanes. A more highly developed toolbox for the use of sugar silanes as glycosyl donors provides greater flexibility in the assembly of glycosidic bonds and a number of advances are reported. Expanding upon the hydrosilylation of

ketones and the reductive coupling of aldehydes and alkynes, alcohols are now accessible as glycosyl acceptors using sugar silanes. Typically the most utilized glycosyl acceptor functional group for the formation of *O*-glycosides, the inclusion of alcohols as suitable substrates for catalytic dehydrogenative silylation with sugar silanes provides the benefit of high anomeric diastereoselectivity through intramolecular delivery while avoiding the formation of wasteful substitution byproducts. Additionally, the identification of $B(C_6F_5)_3$ as a catalyst for the selective dehydrogenative silylation of primary alcohols over secondary alcohols provides a valuable tool for the synthesis of glycosides bearing multiple alcohol functionalities on the glycosyl acceptor. While many routes to these glycosides have been shown to require the use of wasteful protecting group steps to mask undesired reactivity, the selection of a suitable catalyst for reaction with sugar silanes renders these steps unnecessary.

In addition to α-glucosides and β-mannosides achieved by tethering to the C2 hydroxyl, products now include β-glycosides through intramolecular delivery from the C6 hydroxyl. This is the first general strategy to obtain 1,2-*trans* glycosides through intramolecular delivery. The use of a 1,2-*trans* diol protecting group is an innovative tool to instill rigidity to the glycosyl donor and inhibit the formation of 1,6-anhydro byproducts. The formation of β-glucosides intermolecularly is typically limited to donor substrates which bear participating protecting groups at the C2 hydroxyl. Delivery from the C6 hydroxyl using sugar silanes provides β-glucosides with complete selectivity regardless of the C2 hydroxyl protecting group. Furthermore, 2-azido and 2-deoxy sugars undergo this transformation to provide only the β-glycoside. These results represent a significant advancement in the use of sugar silanes, giving access to three of the four

possible 1,2-stereochemistries of glycosides and allowing the use of alcohols as glycosyl acceptors.

Chapter 4
Experimental Procedures and Spectral Data

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, Inc., Model # SPS-400-3 and PS-400-3). Copper (I) chloride (CuCl, Strem, used as received), 1,3-bis-(2,6-diisopropylphenyl)-imidazolium chloride (IPr•HCl, Aldrich, used as received), chloro[1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene]copper (CuCl•IPr, Aldrich, used as received), 1,3-dimesitylimidazolium chloride (IMes•HCl, Strem, used as received), postassium *tert*-butoxide (KO*t*Bu, Strem, used as received), and sodium *tert*-butoxide (NaO*t*Bu, Aldrich, used as received) were stored and weighed in an inert atmosphere glovebox. Tris(pentafluorophenyl)borane ($B(C_6F_5)_3$, Aldrich, used as received) was stored and weighed in an inert atmosphere glovebox but was also found to perform equally well when stored in a vial kept in a desiccator and weight on the benchtop. Chlorodimethylsilane (Me_2SiHCl, Aldrich) was distilled under N_2 and transferred to a Schlenk flask at 0 °C for storage. Triethylamine (NEt_3, Aldrich) was freshly distilled under N_2 prior to use. Trimethylsilyltrifluoromethylsulfonate (TMSOTf, Aldrich) was distilled under vacuum and transferred to a Schlenk tube for storage. All $B(C_6F_5)_3$ and Cu-NHC reactions were conducted in flame dried glassware under a nitrogen atmosphere. Powdered 4 Å molecular sieves were dried overnight before use at 150 °C at less than 1 torr and stored in an oven at 130 °C. ^{1}H and ^{13}C spectra were

obtained in $CDCl_3$ or CD_3OD on a Varian Mercury 400, Varian Unity 500, Varian vnmrs 500, or Varian vnmrs 700 MHz instrument. Chemical shifts of ^1H NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (7.25 ppm) or CD_3OD (3.31 ppm) on the δ scale. Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) or CD_3OD (49.0 ppm) on the δ scale. NMR spectra are described using first order analysis. High resolution mass spectra (HRMS) were obtained on a VG-70-250-S spectrometer manufactured by Micromass Corp. (Manchester, UK) at the University of Michigan Mass Spectrometry Laboratory.

General Procedure A – Preparation of Sugar Silanes

The respective 2-OH or 6-OH sugar (1.0 equiv) was dissolved in dry CH_2Cl_2 (0.2 M) and cooled to 0 °C in an ice bath. Freshly distilled NEt_3 (2.0 equiv) was added and stirred for 3 min, then Me_2SiHCl (1.5 equiv) was added. The reaction was allowed to stir for 4 h. Volatiles were removed by rotary evaporation. The resulting oil was extracted from $NaHCO_3$ (aq.) (diluted over ice) 3 times with CH_2Cl_2. The combined organic extracts were dried quickly over $MgSO_4$, filtered, concentrated, and the resulting solid or oil was stored under vacuum or frozen in C_6H_6. Note – the sugar silanes are stable for months when stored frozen in benzene or under high vacuum. Alternatively, the corresponding 2-OH or 6-OH sugars are very stable to be stored for long periods of time on the bench top.

General Procedure B – $B(C_6F_5)_3$ Promoted Coupling of Alcohols and Sugar Silanes

A mixture of sugar silane (1.0-1.5 equiv) and alcohol (1.0 equiv) was dissolved in dry toluene (0.1 M) at rt under an inert atmosphere (N_2) and stirred until both substrates

were completely dissolved. $B(C_6F_5)_3$ (2-4 mol%) was added as a solid under a gentle stream of nitrogen followed by re-attachment of the septum and nitrogen line. Alternatively, a mixture of alcohol (1.0 equiv) and $B(C_6F_5)_3$ (5 mol%) were dissolved in dry toluene (0.1 M) at rt under an inert atmosphere (N_2) with 4 Å MS (400 mg/mmol). Sugar silane (1.5 equiv) was dissolved in toluene (0.5 – 0.75 M) and added slowly over 1 h. Upon completion of the reaction as monitored by TLC, the reaction mixture was either loaded directly onto a column or the volatiles were removed by rotary evaporation and then loaded onto a column for purification by flash chromatography (SiO_2) to afford the desired product. Note – dry CH_2Cl_2 was found to be the optimal co-solvent if a substrate is marginally soluble in toluene.

General Procedure C – CuCl/NHC•HCl and CuCl•NHC Promoted Dehydrogenative Silylation of Alcohols with Sugar Silanes

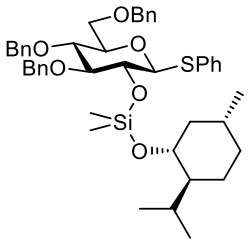
A solid mixture of CuCl (5 mol%), NHC•HCl (5 – 10 mol%), and KO*t*Bu or NaO*t*Bu (5 – 10 mol%) was dissolved in dry $PhCH_3$ (0.015 M) at rt under an inert atmosphere (N_2) and stirred for 15 min. A mixture of alcohol (1.0 equiv), silane (1.1 equiv), and 4 Å MS (0 – 400 mg/mmol) was dissolved in dry $PhCH_3$ (0.1 – 0.2 M) and the catalyst was added to this mixture as a solution in dry $PhCH_3$. Upon completion of the reaction as monitored by TLC, the reaction mixture was filtered through a short plug of silica gel with 50% EtOAc/hex and concentrated by rotary evaporation. The resulting residue was purified via flash chromatography (SiO_2) to afford the desired product.

Alternatively, a solid mixture of CuCl•NHC (5 mol%) and KO*t*Bu or NaO*t*Bu (5 mol%) can be used in the above procedure.

General Procedure D – NIS-TMSOTf Promoted Glycosylation of Silyl-Linked Compounds

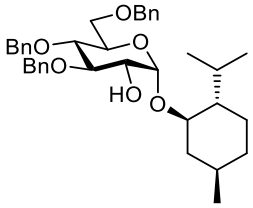
The respective silyl-linked compound (1.0 equiv) was dissolved in dry CH_2Cl_2 (0.02 M) and cooled to -78 or -40 °C. *N*-iodosuccinimide (1.3 – 1.4 equiv) and 2,6-DTBMP (2.0 – 4.0 equiv) were added and stirred for 3 – 5 min. To this solution was added TMSOTf (1.2 – 2.4 equiv) and the reaction was stirred for 5 – 20 min followed by warming to 0 °C unless otherwise noted. Upon disappearance of the silyl-linked compound as monitored by TLC, TBAF (5 equiv, 1 M in THF) was added and the reaction was warmed to rt and stirred overnight. The reaction mixture was quenched with $Na_2S_2O_3$ (sat. aq.) and extracted three times from NH_4Cl (sat. aq.) with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The resulting residue was purified by flash chromatography (SiO_2) to afford the desired product. Note – All experimentals include a bolded diagnostic ^{1}H NMR peak for the assignment of anomeric stereochemistry.

1



Following general procedure B, glucose C2 sugar silane (60 mg, 0.10 mmol), (-)-menthol (16 mg, 0.10 mmol), and $B(C_6F_5)_3$ (2 mg, 0.004 mmol) were stirred for 85 min at rt. The product (73 mg, 0.097 mmol, 97%) was obtained as a colorless oil upon purification by flash chromatography (5 to 8% EtOAc/hex on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-

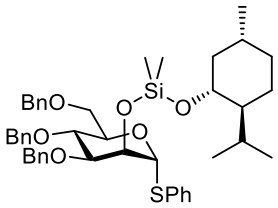
7.56 (m, 2H), 7.38-7.41 (m, 2H), 7.21-7.35 (m, 14H), 7.14-7.17 (m, 2H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 9.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 10.5 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.76-3.81 (m, 2H), 3.71 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.53-3.66 (m, 4H), 2.21 (septd, *J* = 7.0, 2.5 Hz, 1H), 2.01 (d, *J* = 12.0 Hz, 1H), 1.53-1.63 (m, 2H), 1.28-1.37 (m, 1H), 1.12 (dt, *J* = 12.5, 3.0 Hz, 1H), 1.05 (q, *J* = 12.5 Hz, 1H), 0.86-0.97 (m, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.72-0.82 (m, 1H), 0.74 (d, *J* = 7.0 Hz, 3H), 0.25 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.2, 138.0, 134.5, 131.1, 128.9, 128.4, 128.3, 128.2, 127.8, 127.73, 127.66, 127.52, 127.50, 127.3, 127.0, 88.8, 87.0, 79.0, 78.2, 75.2, 74.9, 73.9, 73.4, 72.7, 69.0, 49.7, 45.4, 34.5, 31.6, 25.2, 22.8, 22.2, 21.2, 15.9, -1.2,-1.4; IR (film, cm^{-1}) 3030, 2953, 2919, 2868, 1453, 1365, 1254, 1067; HRMS (ES) *m/z* calcd for $C_{45}H_{58}O_6SSi$ $[M+Na]^+$ 777.3621, found 777.3622.



Following general procedure D, the previous tethered intermediate (148 mg, 0.20 mmol), NIS (57 mg, 0.25 mmol), TMSOTf (43 μL, 0.24 mmol), and 2,6-DTBMP (80 mg, 0.39 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C and stirred for 30 min, and quenched with TBAF. The product (113 mg, 0.19 mmol, 98%) was obtained as a colorless oil upon purification by flash chromatography (10% EtOAc/hex) on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.25-7.37 (m, 11H), 7.14-7.17 (m, 2H), **4.99 (d, *J* = 4.5 Hz, 1H)**, 4.97 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 10.0 Hz,

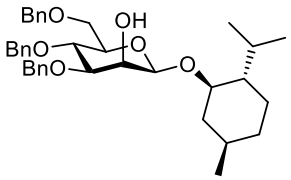
1H), 3.94 (ddd, *J* = 10.0, 3.5, 2.0 Hz, 1H), 3.77 (dd, *J* = 10.75, 4.25 Hz, 1H), 3.60-3.74 (m, 4H), 3.40 (td, *J* = 10.5, 4.0 Hz, 1H), 2.19 (d, *J* = 12.5 Hz, 1H), 2.14 (septd, *J* = 6.5, 2.5 Hz, 1H), 1.96 (d, *J* = 9.0 Hz, 1H), 1.61-1.68 (m, 2H), 1.34-1.45 (m, 1H), 1.25-1.33 (m, 1H), 0.94-1.06 (m, 2H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.78-0.86 (m, 1H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.2, 138.0, 128.4, 128.3, 128.0, 127.92, 127.86, 127.7, 127.64, 127.60, 100.0, 83.5, 81.1, 77.4, 75.2, 75.0, 73.6, 73.5, 70.6, 68.6, 48.7, 42.9, 34.1, 31.6, 25.5, 22.8, 22.2, 21.2, 15.7; IR (film, cm^{-1}) 3566, 3062, 3030, 2922, 2868, 1454, 1362, 1133, 1067, 1028; HRMS (ES) *m/z* calcd for $C_{37}H_{48}O_6$ $[M+Na]^+$ 611.3349, found 611.3354.

2



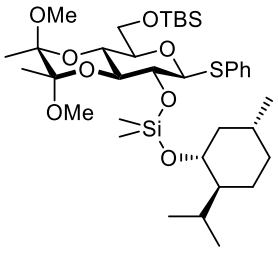
Following general procedure B, mannose C2 sugar silane (60 mg, 0.10 mmol), (-)-menthol (16 mg, 0.10 mmol), and $B(C_6F_5)_3$ (2 mg, 0.004 mmol) were stirred at rt for 1.5 h. The product (62 mg, 0.082 mmol, 92%) was obtained as a colorless oil upon purification by flash chromatography (5 to 8% EtOAc/hex) on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.51 (m, 2H), 7.38-7.42 (m, 2H), 7.20-7.36 (m, 16H), 5.53 (s, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.47 (s, 1H), 4.30 (dd, *J* = 9.5, 5.0 Hz, 1H), 4.00 (t, *J* = 9.5 Hz, 1H), 3.85 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.80 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.76 (d, *J* = 11.0 Hz, 1H), 3.54 (td, *J* = 10.0, 4.5 Hz, 1H), 2.09-2.19 (m, 1H), 1.95 (d, *J* = 12.0 Hz, 1H), 1.52-1.63 (m, 2H), 1.25-1.35 (m, 1H), 1.08-1.16 (m, 1H), 1.01 (q, *J* = 12.0 Hz,

1H), 0.75-0.87 (m, 7H), 0.72 (d, J = 7.0 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 138.3, 134.7, 131.4, 128.9, 128.3, 128.2, 127.92, 127.86, 127.63, 127.57, 127.3, 127.1, 89.0, 80.3, 75.0, 74.9, 73.2, 73.0, 72.6, 72.2, 70.8, 69.3, 49.8, 45.3, 34.5, 31.6, 25.3, 22.8, 22.2, 21.1, 15.9, -1.35, -1.40; IR and HRMS match previously reported data for a mixture of diastereomers at the (-)-menthol carbinol.[83]



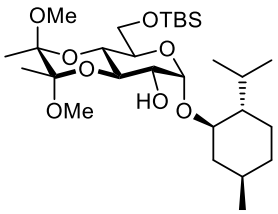
Following general procedure D, the previous tethered intermediate (130 mg, 0.17 mmol), NIS (50 mg, 0.22 mmol), TMSOTf (37 μL, 0.21 mmol), and 2,6-DTBMP (70 mg, 0.34 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C and stirred for 90 min, and quenched with TBAF. The product (100 mg, 0.17 mmol, 98%) was obtained as a white solid upon purification by flash chromatography (10 to 20% EtOAc/hex) on SiO_2. All spectral data matches previously reported data.[83]

3



Following general procedure C, cyclic acetal and TBS protected glucose sugar silane (61 mg, 0.11 mmol), (-)-menthol (16 mg, 0.10 mmol), CuCl (0.5 mg, 0.005 mmol), IMes•HCl (1.7 mg, 0.005 mmol), and NaO*t*Bu (1 mg, 0.010 mmol) were stirred at rt for 1

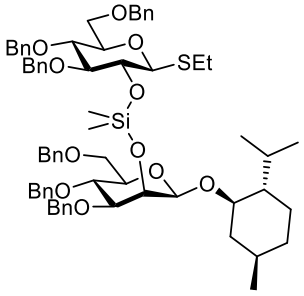
hr. The product (72 mg, 0.010 mmol, 99%) was obtained as a colorless oil upon purification by flash chromatography (5 to 8% EtOAc/hex) on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.54 (m, 2H), 7.20-7.29 (m, 3H), 4.63 (d, *J* = 8.5 Hz, 1H), 3.87 (dd, *J* = 11.5, 1.5 Hz, 1H), 3.81 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.66-3.75 (m, 3H), 3.62 (td, *J* = 10.5, 4.5 Hz, 1H), 3.46 (ddd, *J* = 9.0, 4.5, 2.0 Hz, 1H), 3.29 (s, 3H), 3.27 (s, 3H), 2.21 (septd, *J* = 7.5, 2.0 Hz, 1H), 2.03-2.09 (m, 1H), 1.54-1.64 (m, 2H), 1.24-1.36 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.15 (ddt, *J* = 12.0, 9.5, 2.5 Hz, 1H), 0.76-1.02 (m, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.73 (d, *J* = 7.0 Hz, 3H), 0.21 (s, 3H), 0.20 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 130.9, 128.7, 126.8, 99.6, 99.3, 89.2, 78.5, 74.5, 72.5, 70.7, 65.1, 61.5, 49.9, 48.0, 48.0, 45.2, 34.5, 31.6, 25.9, 25.1, 22.9, 22.2, 21.3, 18.3, 17.6, 17.5, 16.0, -0.3, -1.8, -5.1, -5.5; IR (film, cm^{-1}) 2955, 2929, 2870, 1462, 1371, 1255, 1139, 1072, 1042; HRMS (ES) *m/z* calcd for $C_{26}H_{46}O_7SSi_2$ $[M+NH_4]^+$ 730.4199, found 730.4195.



Following general procedure D, the previous tethered intermediate compound **4c** (67 mg, 0.094 mmol), NIS (27 mg, 0.122 mmol), TMSOTf (20 μL, 0.113 mmol), and 2,6-DTBMP (39 mg, 0.188 mmol) were stirred for 10 min at -40 °C, warmed to 0 °C and stirred for 65 min, and quenched with TBAF. The product (33 mg, 0.06 mmol, 60%) was obtained as a colorless oil upon purification by flash chromatography (10 to 15% EtOAc/hex) on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ **4.96 (d, *J* = 4.0 Hz, 1H)**, 3.76-3.89 (m, 4H), 3.61-3.68 (m, 3H), 3.40 (dt, *J* = 10.5, 4.0 Hz, 1H), 3.32 (s, 3H), 3.27 (s, 3H),

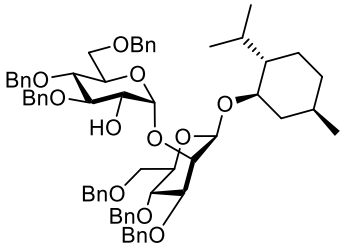
2.08-2.21 (m, 2H), 1.91 (d, *J* = 10.5 Hz, 1H), 1.56-1.67 (m, 2H), 1.34-1.42 (m, 1H), 1.36 (s, 3H), 1.24-1.32 (m, 1H), 1.31 (s, 3H), 0.76-1.05 (m, 6H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.79 (d, *J* = 7.0, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.65, 99.60, 99.4, 80.6, 70.74, 70.68, 70.4, 65.7, 61.5, 48.8, 48.0, 47.9, 42.8, 34.2, 31.6, 25.9, 25.7, 23.0, 22.3, 21.1, 17.8, 17.7, 15.8, -5.1, -5.4; IR (film, cm^{-1}) 3490, 2954, 2930, 2871, 1638, 1458, 1376, 1252, 1138, 1035; HRMS (ES) *m/z* calcd for $C_{28}H_{40}O_8Si$ $[M+Na]^+$ 569.3480, found 569.3481.

4



Following general procedure C, glucose C2 sugar silane (27 mg, 0.049 mmol), **2** (29 mg, 0.049 mmol) and $B(C_6F_5)_3$ (2 mg, 0.004 mmol) were stirred at rt overnight. The product (38 mg, 0.033 mmol, 68%) was obtained as an oil upon purification by flash chromatography (10% EtOAc/hex) on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.35-7.38 (m, 2H), 7.18-7.34 (m, 22H), 7.12-7.15 (m, 2H), 7.06-7.10 (m, 2H), 5.22 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.69 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.423 (d, *J* = 12.0 Hz, 1H), 4.421 (d, *J* = 10.0 Hz, 1H), 4.39 (s, 1H), 4.36 (d, *J* = 9.5 Hz, 1H), 4.23 (d, *J* = 11.0 Hz, 1H), 4.17 (d, *J* = 2.5 Hz, 1H), 3.96 (dd, *J* = 9.5, 8.5 Hz, 1H), 3.73 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.44-3.66 (m, 8H), 3.32-3.38 (m, 1H), 3.28 (dd, *J* = 10.5, 7.0 Hz, 1H), 2.73 (dq, *J* =

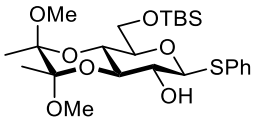
13.0, 7.5 Hz, 1H), 2.68 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.57 (septd, *J* = 6.5, 2.0 Hz, 1H), 1.96 (d, *J* = 12.5 Hz, 1H), 1.60-1.68 (m, 2H), 1.27-1.40 (m, 1H), 1.28 (t, *J* = 7.5 Hz, 3H), 1.16-1.24 (m, 1H), 0.77-1.03 (m, 3H), 0.904 (d, *J* = 7.0 Hz, 3H), 0.900 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.31 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.60, 138.56, 138.5, 138.32, 138.31, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.53, 127.46, 127.42, 127.36, 127.2, 96.7, 87.4, 86.2, 82.4, 79.1, 78.0, 76.3, 75.6, 75.4, 75.1, 75.0, 74.8, 74.6, 73.3, 71.2, 70.7, 70.1, 69.3, 47.9, 40.9, 34.4, 31.3, 24.7, 24.5, 22.8, 22.3, 21.6, 15.8, 15.2, -0.7, -1.1; IR (film, cm^{-1}) 3062, 3030, 2953, 2918, 2850, 1652, 1454, 1368, 1254, 1095, 1067, 872, 849, 792, 735, 697; HRMS (ES) *m/z* calcd for $C_{68}H_{86}O_{11}SSi$ $[M+NH_4]^+$ 1156.5998, found 1156.5991.



Following general procedure D, the previous tethered intermediate (37 mg, 0.032 mmol), NIS (9.5 mg, 0.042 mmol), TMSOTf (7.0 μL, 0.039 mmol), and 2,6-DTBMP (13 mg, 0.065 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C and stirred for 1.5 h, and quenched with TBAF. The product (29 mg, 0.028 mmol, 89%) was obtained as a colorless oil upon purification by flash chromatography (20% EtOAc/hex) on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.39 (m, 27H), 7.16-7.21 (m, 3H), **5.12 (d, *J* = 3.0 Hz, 1H)**, 4.90 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 10.5 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.61-4.70 (m, 4H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.41 (s, 1H), 4.27 (d, *J* = 9.5 Hz, 1H), 3.92 (d, *J* = 2.5 Hz, 1H), 3.83 (t, *J* = 9.75 Hz, 1H), 3.70-3.81 (m, 6H), 3.58-3.64

(m, 2H), 3.44 (td, *J* = 11.0, 4.0 Hz, 1H), 3.38 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.15 (d, *J* = 7.5 Hz, 1H), 2.30 (sept, *J* = 6.5 Hz, 1H), 1.91 (d, *J* = 12.5 Hz, 1H), 1.58-1.70 (m, 2H), 1.28-1.40 (m, 1H), 1.05-1.12 (m, 1H) 0.73-1.00 (m, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 7.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.9, 138.5, 138.1, 138.0, 137.3, 128.6, 128.4, 128.32, 128.28, 128.25, 128.17, 128.1, 128.0, 127.90, 127.88, 127.87, 127.8, 127.60, 127.56, 127.4, 127.34, 127.26, 100.9, 96.9, 83.9, 82.3, 76.9, 75.6, 75.2, 75.1, 74.9, 74.7, 74.1, 73.6, 73.5, 72.8, 70.5, 69.7, 68.5, 48.0, 41.0, 34.3, 31.4, 24.8, 22.7, 22.2, 21.1, 15.7; IR (film, cm^{-1}) 3428, 3031, 2923, 2867, 1727, 1453, 1273, 1095, 1054; HRMS (ES) *m/z* calcd for $C_{64}H_{76}O_{11}$ $[M+Na]^+$ 1043.5285, found 1043.5297.

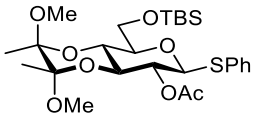
18



To a solution of 3,4-*O*-(2',3'-dimethoxybutane-2',3'-diyl)-thio-*β*-D-glycoside[102] (6.3 g, 16.3 mmol) in pyridine (82 mL, 0.2 M) was added TBSCl (2.7 g, 18.0 mmol). The solution was stirred for 4 h and then quenched with MeOH, diluted with Et_2O, washed with H_2O (x3), dried over $MgSO_4$, filtered, and concentrated to give the product (6.4g, 12.8 mmol, 78%) as a white foam. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.7, 1.4 Hz, 2H), 7.25-7.32 (m, 3H), 4.53 (d, *J* = 9.1 Hz), 3.89 (dd, *J* = 11.2, 1.4 Hz), 3.84 (dd, *J* = 11.2, 3.5 Hz, 1H), 3.69-3.77 (m, 2H), 3.50 (t, *J* = 9.1 Hz), 3.31 (s, 3H), 3.26 (s, 3H), 2.40 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 133.2, 131.6, 128.9, 128.1, 99.7, 99.4, 88.4, 78.9, 73.7, 69.2, 64.7, 61.2, 48.1, 47.9, 25.9, 18.4, 17.7, 16.6, -5.1, -5.4; IR (film, cm^{-1}) 3350, 2947, 2040, 1472,

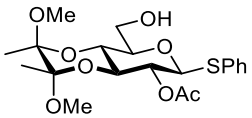
1252, 1117, 1074, 1022; HRMS (ES) *m/z* calcd for $C_{24}H_{40}O_7SSi$ $[M+Na]^+$ 523.2156, found 523.2155.

19



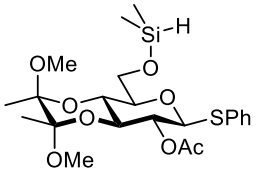
To a solution of **18** (1.66 g, 3.3 mmol) in pyridine (6.6 mL, 0.5 M) was added acetic anhydride (6.6 mL, 0.5 M) and the reaction was stirred overnight. The reaction was diluted with ethyl acetate, washed with H_2O, washed with sat. aq. NH_4Cl (x3), dried over $MgSO_4$, filtered, and concentrated. The crude mixture was subjected to flash chromatography (15 to 30% EtOAc/hex) to give the product (1.69 g, 3.1 mmol, 94%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.54 (m, 2H), 7.25-7.31 (m, 3H), 4.97 (t, *J* = 9.5 Hz, 1H), 4.65 (d, *J* = 9.5 Hz, 1H), 3.89 (dd, *J* = 11.5, 2 Hz, 1H), 3.74-3.86 (m, 3H), 3.48 (ddd, *J* = 9.5, 4.5, 2 Hz, 1H), 3.25 (s, 3H), 3.24 (s, 3H), 2.12 (s, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.2, 133.1, 132.3, 128.8, 127.7, 99.7, 99.5, 86.4, 78.8, 72.1, 69.3, 65.0, 61.3, 48.0, 47.6, 25.9, 20.9, 18.3, 17.61, 17.57, -5.08, -5.45; IR (film, cm^{-1}) 2987, 2950, 2855, 1744, 1584, 1464, 1367, 1277, 1242, 1071; HRMS (ES) *m/z* calcd for $C_{26}H_{42}O_8SSi$ $[M+NH_4]^+$ 560.2708, found 560.2721.

20



To a solution of **15** (1.69 g, 3.1 mmol) in CH_2Cl_2 (10 mL, 0.3 M) was added TBAF (1.0 M in THF, 9.3 mL, 9.3 mmol) and the reaction was stirred for 3 h. The reaction was poured into H_2O and extracted with CH_2Cl_2 (x3), dried over $MgSO_4$, filtered, and concentrated. The crude mixture was subjected to flash chromatography (20 to 30% EtOAc/hex) to give the product (1.07 g, 2.5 mmol, 80%) as a colorless amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.46 (m, 2H), 7.19-7.29 (m, 3H), 4.92 (t, *J* = 9.6 Hz, 1H), 4.64 (d, *J* = 9.6 Hz, 1H), 3.74-3.88 (m, 2H), 3.65 (t, *J* = 9.6 Hz, 2H), 3.47-3.56 (m, 1H), 3.18 (s, 3H), 3.16 (s, 3H), 2.29 (br s, 1H), 2.06 (s, 3H), 1.207 (s, 3H), 1.205 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.1, 132.4, 132.3, 128.9, 127.9, 99.7, 99.5, 86.1, 78.1, 71.6, 69.2, 65.6, 61.2, 47.8, 47.5, 20.8, 17.54, 17.48; IR (film, cm^{-1}) 3509, 2994, 2951, 2836, 2249, 1754, 1585, 1440, 1370, 1224, 1134, 1035; HRMS (ES) *m/z* calcd for $C_{20}H_{28}O_8S$ $[M+NH_4]^+$ 451.1408, found 451.1408.

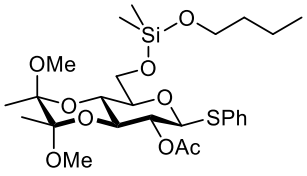
21



Following general procedure A, **7b** (1.04 g, 2.2 mmol), NEt_3 (0.61 mL, 4.3 mmol), and Me_2SiHCl (0.36 mL, 3.3 mmol) were stirred at 0 °C for 3 h. The product (1.13g, 2.1 mmol, 98%) was obtained as a white solid without further purification. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.48-7.52 (m, 2H), 7.25-7.29 (m, 3H), 4.95 (t, *J* = 9.8 Hz, 1H), 4.64 (sep, *J* = 2.8 Hz, 1H), 4.62 (d, *J* = 9.8 Hz, 1H), 3.89 (dd, *J* = 11.2, 1.4 Hz, 1H), 3.78-3.84 (m, 2H), 3.72 (t, *J* = 9.8 Hz, 1H), 3.50 (ddd, *J* = 9.8, 5.6, 1.4 Hz, 1H), 3.22 (s, 3H), 3.21 (s, 3H), 2.10 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 0.20 (d, *J* = 2.8 Hz, 3H), 0.19 (d, *J* = 2.8 Hz,

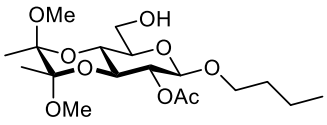
3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.1, 132.7, 132.6, 128.7, 127.8, 99.8, 99.5, 86.2, 78.6, 71.9, 69.3, 65.2, 62.4, 47.9, 47.6, 20.9, 17.60, 17.55, -1.39, -1.41; IR (film, cm^{-1}) 2992, 2951, 2833, 2113, 1752, 1368, 1223, 1127, 1066; HRMS (ES) *m/z* calcd for $C_{22}H_{34}O_8SSi$ $[M+Na]^+$ 509.1636, found 509.1636.

26



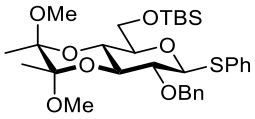
Following general procedure C, **21** (54 mg, 0.11 mmol), butanol (9.2 μL, 0.1 mmol), CuCl (0.5 mg, 0.005 mmol), IPr•HCl (4.3 mg, 0.01 mmol), NaOtBu (1 mg, 0.01 mmol), and 4Å molecular sieves (40 mg) were stirred overnight. The product (48 mg, 0.086 mmol, 86%) was obtained as a colorless oil upon flash chromatography (10 to 15% EtOAc/hex) on SiO_2. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.47-7.51 (m, 2H), 7.22-7.28 (m, 3H), 4.96 (t, *J* = 9.8 Hz, 1H), 4.64 (d, *J* = 9.8 Hz, 1H), 3.96 (dd, *J* = 11.2, 1.4 Hz, 1H), 3.79-3.85 (m, 2H), 3.75 (t, *J* = 9.8 Hz, 1H), 3.66 (t, *J* = 7.0 Hz, 1H), 3.51 (ddd, *J* = 9.8, 4.9, 1.4 Hz, 1H), 3.23 (s, 3H), 3.22 (s, 3H), 2.01 (s, 3H), 1.50 (quin, *J* = 7.0 Hz, 2H), (sex, *J* = 7.0 Hz, 2H), 1.26 (s, 3H), 1.25 (s, 3H), 0.88 (t, *J* = 7.7 Hz, 3H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.2, 133.1, 132.2, 128.8, 127.6, 99.8, 99.5, 86.2, 78.5, 71.9, 69.3, 65.2, 62.3, 60.7, 47.9, 47.6, 34.7, 20.9, 18.9, 17.61, 17.57, 13.9, -3.0, -3.2; IR (film, cm^{-1}) 2955, 2932, 1754, 1368, 1255, 1223, 1128, 1071, 1034, 849; HRMS (ES) *m/z* calcd for $C_{26}H_{42}O_9SSi$ $[M+NH_4]^+$ 576.2657, found 576.2649.

38



Following general procedure D, **26** (46 mg, 0.082 mmol), NIS (24 mg, 0.110 mmol), 2,6-DTBMP (34 mg, 0.160 mmol), and TMSOTf (18 μL, 0.010 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C for 3 h, and quenched with TBAF. The product (24 mg, 0.061 mmol, 75%) was obtained as a white solid upon flash chromatography (20 to 30% EtOAc/hex) on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (dd, *J* = 10.0, 8.0 Hz, 1H), **4.44 (d, *J* = 8.0 Hz, 1H)**, 3.71-3.91 (m, 5H), 3.52 (ddd, *J* = 9.0, 4.5, 3.0 Hz, 1H), 3.46 (dt, *J* = 9.5, 7.0 Hz, 1H), 3.25 (s, 3H), 3.24 (s, 3H), 2.08 (s, 3H), 2.00 (s, 1H), 1.46-1.62 (m, 2H), 1.24-1.42 (m, 2H), 1.29 (s, 3H), 1.28 (s, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 101.8, 99.64, 99.55, 73.9, 70.7, 70.1, 69.8, 65.9, 61.2, 47.9, 47.6, 31.4, 20.8, 18.9, 17.6, 17.5, 13.7; IR (film, cm^{-1}) 3492, 2956, 1748, 1457, 1370, 1228, 1127, 906, 730; HRMS (ES) *m/z* calcd for $C_{18}H_{32}O_9$ $[M+NH_4]^+$ 410.2385, found 410.2384.

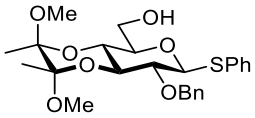
47



A solution of **18** (4.8 g, 9.6 mmol) and BnBr (1.37 mL, 11.5 mmol) in DMF (24 mL, 0.4 M) was cooled to 0 °C and NaH (500mg, 21 mmol) was added. The solution was stirred at rt for 1 h and quenched with MeOH, diluted with EtOAc (100 mL), washed with H_2O (5 x 70 mL), dried over $MgSO_4$, filtered, and concentrated. The product (5.2 g, 8.9 mmol, 92%) was obtained without further purification as a white foam. ^{1}H NMR (700 MHz,

$CDCl_3$) δ 7.54-7.58 (m, 2H), 7.39-7.44 (d, *J* = 7.0 Hz, 2H), 7.30-7.35 (t, *J* = 7.0 Hz, 2H), 7.23-7.29 (m, 4H), 4.80 (d, *J* = 10.5 Hz, 1H), 4.69 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 9.1 Hz, 1H), 3.80-3.90 (m, 3H), 3.76 (t, *J* = 9.8 Hz, 1H), 3.46 (t, *J* = 9.8 Hz, 1H), 3.42 (d, *J* = 9.1 Hz, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.5, 133.4, 132.5, 128.8, 128.3, 128.1, 127.7, 127.5, 99.6, 99.4, 87.4, 78.5, 77.4, 75.4, 75.0, 64.9, 61.2, 48.1, 47.9, 25.9, 18.4, 17.8, 17.6, -5.1, -5.45; IR (film, cm^{-1}) 3440, 2927, 1641, 1471, 1376, 1252, 1133, 1048; HRMS (ES) *m/z* calcd for $C_{31}H_{46}O_7SSi$ $[M+NH_4]^+$ 608.3072, found 608.3074.

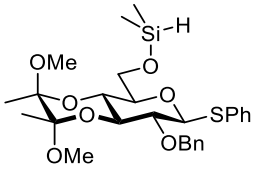
45



To a solution of **47** (5.1 g, 8.7 mmol) in CH_2Cl_2 (35 mL, 0.25 M) was added TBAF (1 M in THF, 13.0 mL, 13.0 mmol). The reaction was stirred at rt for 3 h and quenched with H_2O, extracted with CH_2Cl_2 (x3), the organic layers combined, dried over $MgSO_4$, filtered, and concentrated. The crude mixture was subjected to flash chromatography (20 to 40% EtOAc/hex) and recrystallized (H_2O/EtOH) to give the product (3.7 g, 7.7 mmol, 89%) as white crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.54 (m, 2H), 7.43-7.47 (m, 2H), 7.34-7.39 (m, 2H), 7.29-7.34 (m, 2H), 4.87 (d, *J* = 10.5 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 9.5 Hz, 1H), 3.87-3.94 (m, 2H), 3.74 (dd, *J* = 12.0, 5.0 Hz, 1H), 3.71 (t, *J* = 10 Hz, 1H), 3.55 (ddd, *J* = 5.0, 4.5, 3.0 Hz, 1H), 3.49 (t, *J* = 9.5 Hz, 1H), 3.29 (s, 3H), 3.29 (s, 3H), 1.89 (s, 1H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 132.7, 132.6, 129.0, 128.3, 128.2, 127.9, 127.8, 99.7, 99.5, 87.2, 77.6, 77.5, 75.5, 74.6, 65.8, 61.5, 48.02, 47.95, 17.8, 17.6; IR (film, cm^{-1}) 3502, 2948, 2360,

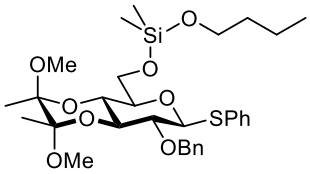
1652, 1456, 1377, 1132; HRMS (ES) *m/z* calcd for $C_{25}H_{32}O_7S$ $[M+NH_4]^+$ 494.2207, found 494.2213.

46



Following general procedure A, **45** (1.04 g, 2.2 mmol), NEt_3 (0.61 mL, 4.3 mmol), and Me_2SiHCl (0.36 mL, 3.3 mmol) were stirred at 0 °C for 3 h. The product (1.13 g, 2.1 mmol, 98%) was obtained as a white solid after aqueous workup. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55-7.59 (m, 2H), 7.42 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.23-7.30 (m, 4H), 4.80 (d, *J* = 10.5 Hz, 1H), 4.71 (d, *J* = 10.5 Hz, 1H), 4.67 (sep, *J* = 9.8 Hz, 1H), 4.61 (d, *J* = 9.1 Hz, 1H), 3.81-3.92 (m, 3H), 3.73 (t, *J* = 9.8 Hz, 1H), 3.43-3.50 (m, 2 H), 3.27 (s, 3H), 3.26 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 0.22 (d, *J* = 2.8 Hz, 3H), 0.21 (d, *J* = 2.8 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.4, 133.1, 132.7, 128.8, 128.3, 128.1, 127.7, 127.6, 99.6, 99.5, 87.2, 78. 2, 77.4, 75.4, 74.8, 65.1, 62.4, 48.0, 47.9, 17.8, 17.6, -1.37, -1.40; IR (film, cm^{-1}) 2992, 2950, 2835, 2115, 1454, 1376, 1252, 1133, 1077, 1048; HRMS (ES) *m/z* calcd for $C_{27}H_{38}O_7SSi$ $[M+Na]^+$ 557.2000, found 557.2006.

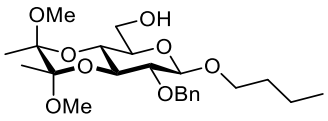
48



Following general procedure C, **46** (118 mg, 0.22 mmol), butanol (18.3 μL, 0.2 mmol), CuCl (0.99 mg, 0.01 mmol), IPr•HCl (8.5 mg, 0.02 mmol), NaOtBu (1.9 mg, 0.02

mmol), and 4Å molecular sieves (80 mg) were stirred overnight. The product (113 mg, 0.19 mmol, 93%) was obtained as a colorless oil upon flash chromatography (5 to 12.5% EtOAc/hex) on SiO_2. ^1H NMR (500 MHz, $CDCl_3$) δ 7.56-7.61 (m, 2H), 7.45 (d, *J* = 7.0 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 2H), 7.26-7.33 (m, 4H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.78 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 9.5 Hz, 1H), 3.99 (d, *J* = 11.0 Hz, 1H), 3.85-3.93 (m, 2H), 3.77 (t, *J* = 10.0 Hz, 1H), 3.70 (t, *J* = 7.0 Hz, 2H), 3.46-3.54 (m, 2H), 3.31 (s, 3H), 3.29 (s, 3H), 1.54 (quin, *J* = 7 Hz, 2H), 1.29-1.40 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 133.4, 132.4, 128.8, 128.3, 128.2, 127.8, 127.5, 99.7, 99.5, 87.2, 78.2, 77.4, 75.4, 74.9, 65.2, 62.3, 60.8, 48.0, 47.9, 34.7, 19.0, 17.9, 17.7, 13.9, -3.0, -3.2; IR (film, cm^{-1}) 2957, 1702, 1454, 1376, 1256, 1036; HRMS (ES) *m/z* calcd for $C_{31}H_{46}O_8SSi$ $[M+NH_4]^+$ 624.3021, found 624.3026.

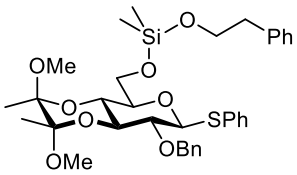
59



Following the general procedure, **48** (57 mg, 0.094 mmol), NIS (27 mg, 0.122 mmol), 2,6-DTBMP (39 mg, 0.188 mmol), and TMSOTf (20 μL, 0.113 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C for 1 h, and quenched with TBAF. The product (15 to 30% EtOAc/hex) was obtained as a colorless oil upon flash chromatography (15 to 30% EtOAc/hex) on SiO_2. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 2 H), 7.27 (t, *J* = 7.0 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.5 Hz, 1H), **4.44 (d, *J* = 7.5 Hz, 1H)**, 3.93 (dt, *J* = 9.5, 6.5 Hz, 1H), 3.88 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.82 (t, *J* = 10.0 Hz, 1H), 3.68-3.78 (m, 2H), 3.48-3.58 (m, 2H), 3.42 (dd, *J* = 9.5,

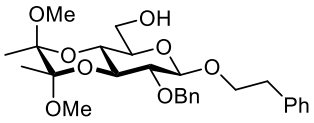
7.5 Hz, 1H), 3.31 (s, 3H), 3.27 (s, 3H), 1.56-1.71 (m, 2H), 1.34-1.51 (m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.7, 128.2, 127.7, 127.5, 103.9, 99.52, 99.47, 79.0, 74.7, 73.6, 72.2, 70.2, 66.1, 61.4, 47.9, 47.8, 31.7, 19.2, 17.8, 17.6, 13.8; IR (film, cm^{-1}) 3491, 3064, 2915, 2246, 1736, 1497, 1454, 1369, 1307; HRMS (ES) *m/z* calcd for $C_{23}H_{36}O_8$ $[M+NH_4]^+$ 458.2748, found 458.2751.

49



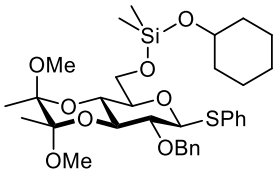
Following general procedure C, **46** (59 mg, 0.11 mmol), phenethyl alcohol (12 μL, 0.1 mmol), CuCl (0.5 mg, 0.005 mmol), IPr•HCl (4.1 mg, 0.01 mmol), NaOtBu (1 mg, 0.01 mmol), and 4Å molecular sieves (40 mg) were stirred overnight. The product (47 mg, 0.072 mmol, 72%) was obtained as a colorless oil upon flash chromatography (5 to 10% EtOAc/hex) on SiO_2. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53-7.57 (m, 2H), 7.41-7.45 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 2H), 7.22-7.30 (m, 6H), 7.17-7.21 (m, 2H), 4.81 (d, *J* = 10.5 Hz, 1H), 4.72 (d, *J* = 10.5 Hz, 1H), 4.63 (d, *J* = 9.8 Hz, 1H), 3.85-3.93 (m, 4H), 3.82 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.74 (t, *J* = 9.8 Hz, 1H), 3.44-3.49 (m, 2H), 3.27 (s, 6H), 2.84 (t, *J* = 7.0 Hz, 2H), 1.35 (s, 3H), 1.29 (s, 3H), 0.093 (s, 3H), 0.089 (s, 3H); ^{13}C NMR (175MHz, $CDCl_3$) δ 138.8, 138.4, 133.4, 132.2, 129.1, 128.8, 128.3, 128.2, 128.1, 127.7, 127.4, 126.1, 99.6, 99.5, 87.2, 78.1, 77.4, 75.4, 74.8, 65.1, 63.6, 60.7, 48.0, 47.9, 39.2, 28.8, 23.8, 23.6, 17.8, 17.6, -3.1, -3.3; IR (film, cm^{-1}) 3064, 3031, 2935, 1679, 1606, 1584, 1472, 1368, 1258, 1136, 1032; HRMS (ES) *m/z* calcd for $C_{35}H_{46}O_8SSi$ $[M+NH_4]^+$ 672.3021, found 672.3021.

61



Following general procedure D, **49** (47 mg, 0.072 mmol), NIS (21 mg, 0.093 mmol), 2,6-DTBMP (29 mg, 0.144 mmol), and TMSOTf (16 μL, 0.086 mmol) were stirred at -40 °C, warmed to 0 °C for 1 h, and quenched with TBAF. The product (30 mg, 0.061 mmol, 86%) was obtained as a colorless oil upon flash chromatography (15 to 25% EtOAc/hex) on SiO_2. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18-7.31 (m, 10H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), **4.45 (d, *J* = 7.7 Hz, 1H)**, 4.13 (dt, *J* = 9.1, 7.0 Hz, 1H), 3.84 (dd, *J* = 11.9, 2.1 Hz, 1H), 3.74-3.81 (m, 2H), 3.67-3.74 (m, 2H), 3.47 (ddd, *J* = 9.8, 4.2, 3.5 Hz, 1H), 3.39 (dd, *J* = 9.8, 7.7 Hz, 1H), 3.28 (s, 3H), 3.26 (s, 3H), 2.95 (t, *J* = 7.0 Hz, 2H), 1.90 (s, 1H), 1.34 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.8, 138.5, 128.9, 128.4, 128.1, 127.6, 127.4, 126.3, 103.9, 99.6, 99.5, 79.0, 74.6, 73.6, 72.1, 71.0, 66.05, 61.4, 47.93, 47.87, 36.2, 17.8, 17.6; IR (film, cm^{-1}) 3494, 2925, 2247, 1497, 1454, 1368, 1329, 1222, 1202, 1132, 1109, 907, 729, 697; HRMS (ES) *m/z* calcd for $C_{27}H_{36}O_8$ $[M+NH_4]^+$ 506.2748, found 506.2759.

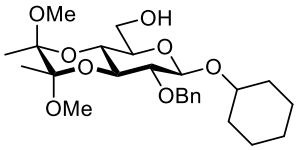
50



Following general procedure C, **46** (59 mg, 0.11 mmol), cyclohexanol (10.6 μL, 0.1 mmol), CuCl (0.5 mg, 0.005 mmol), IPr•HCl (4.1 mg, 0.01 mmol), NaOtBu (1 mg, 0.01 mmol), and 4Å molecular sieves (40 mg) were stirred overnight. The product (51 mg,

0.077 mmol, 78%) was obtained as a colorless oil upon flash chromatography (5 to 10% EtOAc/hex) on SiO_2. ^1H NMR (500 MHz, $CDCl_3$) δ 7.57-7.61 (m, 2H), 7.43-7.47 (m, 2H), 7.33-7.38 (m, 2H), 7.25-7.32 (m, 4H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.73 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 9.5 Hz, 1H), 3.99 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.85-3.93 (m, 2H), 3.71-3.91 (m, 2H), 3.46-3.54 (m, 2H), 3.31 (s, 3H), 3.29 (s, 3H), 1.80-1.90 (m, 2H), 1.67-1.76 (m, 2H), 1.50 (dt, *J* = 12.5, 4.0 Hz, 1H), 1.10-1.40 (m, 5H), 1.37 (s, 3H), 1.31 (s, 3H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 133.5, 132.4, 128.8, 128.3, 128.2, 127.7, 127.5, 99.7, 99.5, 87.2, 78.2, 77.3, 75.4, 74.9, 70.9, 65.2, 60.7, 48.0, 47.9, 35.9, 35.8, 25.5, 24.4, 17.9, 17.7, -2.3, -2.6; IR (film, cm^{-1}) 3063, 2992, 2931, 2857, 2246, 1703, 1585, 1498, 1454, 1376, 1331, 1256, 1219, 1134; HRMS (ES) *m/z* calcd for $C_{33}H_{48}O_8SSi$ $[M+NH_4]^+$ 650.3177, found 650.3185.

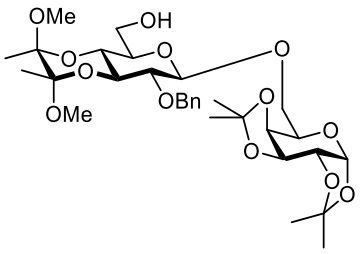
60



Following general procedure D, **50** (49 mg, 0.077 mmol), NIS (23 mg, 1.01 mmol), 2,6-DTBMP (32 mg, 0.155 mmol), and TMSOTf (17 μL, 0.093 mmol) were stirred at 0 °C for 10 min, warmed to 0 °C for 1 h, and quenched with TBAF. The product (40 mg, 0.086, 92%) was obtained as a white solid upon flash chromatography (15 to 20% EtOAc/hex) on SiO_2. ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.25-7.31 (m, 1H), 4.87 (d, *J* = 11.0 Hz), 4.78 (d, *J* = 11.5 Hz, 1H), **4.55 (d, *J* = 7.5 Hz, 1H)**, 3.87 (d, *J* = 12.0 Hz, 1H), 3.81 (t, *J* = 10.0 Hz, 1H), 3.62-3.78 (m, 3H), 3.50 (ddd, *J* = 9.5, 5.0, 3.0 Hz, 1H), 3.41 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.31 (s, 3H), 3.27 (s, 3H), 1.87-2.06 (m, 3H), 1.71-1.84 (m, 2H), 1.51-1.60 (m, 1H), 1.16-1.51 (m, 4 H), 1.36

(s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 128.2, 127.8, 127.5, 102.3, 99.6, 99.5, 79.1, 78.4, 74.8, 73.6, 72.3, 66.3, 61.5, 47.9, 33.8, 32.0, 25.6, 24.1, 24.0, 18.9, 17.8, 17.6; IR (film, cm^{-1}) 3495, 2932, 2353, 1721, 1454, 1374, 1125, 1041; HRMS (ES) *m/z* calcd for $C_{25}H_{38}O_8$ $[M+NH_4]^+$ 484.2905, found 484.2900.

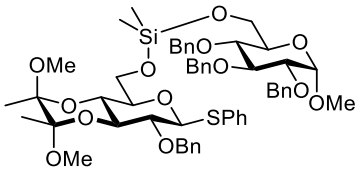
63



Following general procedure C, **46** (59 mg, 0.11 mmol), 1,2:3,4-di-*O*-isopropylidene-galactopyranose (26 mg, 0.1 mmol), CuCl•IPr (2.4 mg, 0.005 mmol), NaOtBu (0.48 mg, 0.005 mmol), and 4Å molecular sieves (40 mg) were stirred overnight. A mixture of the desired silyl-linked intermediate (39 mg, 0.049 mmol, 49%) and the silyl-linked dimer were obtained upon flash chromatography (5 to 15% EtOAc/hex). The mixture was immediately subjected to general procedure D, taking care that all present thiophenyl leaving groups were activated, whereupon NIS (43 mg, 0.190 mmol), 2,6-DTBMP (51 mg, 0.249 mmol), and TMSOTf (32 μL, 0.176 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C for 3 h, and quenched with TBAF. The desired product (26 mg, 0.041 mmol, 41% overall yield) was obtained as a white solid upon flash chromatography (40 to 50% EtOAc/hex) on SiO_2. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 2H), 7.22-7.26 (m, 1H), 5.54 (d, *J* = 4.9 Hz, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 4.74 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 7.7 Hz, 1H), **4.48 (d, *J* = 7.7 Hz, 1H)**, 4.31 (dd, *J* = 2.8, 2.1 Hz, 1H), 4.25 (d, *J* = 9.1 Hz, 1H), 4.05 (dd, *J* = 10.5, 4.9 Hz, 1H), 4.01

(t, *J* = 5.6 Hz, 1H), 3.82-3.89 (m, 1H), 3.80 (t, *J* = 9.8 Hz, 1H), 3.75 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.63-3.71 (m, 2H), 3.46-3.52 (m, 1H), 3.40 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.29 (s, 3H), 3.24 (s, 3H), 1.52 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.322 (s, 3H), 1.316 (s, 3H), 1.28 (s, 3H); ^{13}C (175 MHz, $CDCl_3$) 139.1, 128.1, 127.7, 127.3, 104.4, 99.6, 99.5, 96.4, 78.7, 74.3, 73.7, 72.0, 71.1, 70.7, 70.5, 69.4, 66.8, 66.3, 61.5, 47.89, 47.86, 26.0, 26.0, 25.0, 24.4, 17.8, 17.6; IR (film, cm^{-1}) 3494, 2989, 2933, 1701, 1454, 1376, 1254, 1210, 1133, 1113, 1069, 1045, 1005; HRMS (ES) *m/z* calcd for $C_{31}H_{46}O_{13}$ $[M+K]^+$ 665.2570, found 665.2575.

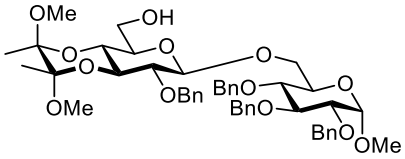
57



Following general procedure B, **46** (48 mg, 0.09 mmol) was slowly added over 1 h to methyl 2,3,4-*O*-tribenzyl-α-D-glucopyranoside (28 mg, 0.06 mmol) and $B(C_6F_5)_3$ and stirred overnight. The product (36 mg, 0.036 mmol, 60%) was obtained as a white solid upon flash chromatography (10 to 18% EtOAc/hex) on SiO_2. ^{1}H NMR (700 Mz, $CDCl_3$) δ 7.52-7.55 (m, 2H), 7.40-7.43 (m, 2H), 7.19-7.36 (m, 21H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.85 (d, *J* = 10.5 Hz, 1H), 4.75-4.81 (m, 3H), 4.70 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.58-4.64 (m, 3H), 3.98 (t, *J* = 9.8 Hz, 1H), 3.94 (dd, *J* = 11.2, 1.4 Hz, 1H), 3.81-3.92 (m, 4H), 3.72 (t, *J* = 9.8 Hz, 1H), 3.62 (dt, *J* = 10.0, 3.0 Hz, 1H), 3.55 (t, *J* = 9.8 Hz, 1H), 3.50 (dd, *J* = 9.8, 4.2 Hz, 1H), 3.41-3.46 (m, 2H), 3.33 (s, 3H), 3.25 (s, 3H), 3.22 (s, 3H), 1.33 (s, 3H), 1.26 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) 138.8, 138.44, 138.38, 138.2, 133.4, 132.3, 128.8, 128.42, 128.39, 128.37, 128.3,

128.1, 128.05, 128.01, 127.8, 127.72, 127.68, 127.62, 127.58, 127.5, 99.6, 99.5, 98.0, 87.3, 82.1, 80.0, 78.1, 77.42, 77.39, 75.8, 75.4, 74.85, 74.81, 73.3, 71.1, 65.1, 61.5, 60.9, 55.0, 48.0, 47.9, 29.7, 17.8, 17.6, -2.9, -3.0; IR (film, cm^{-1}) 2929, 2361, 1585, 1497, 1455, 1366, 1257, 1134, 1048; HRMS (ES) *m/z* calcd for $C_{55}H_{68}O_{13}SSi$ $[M+Na]^+$ 1019.4042, found 1019.4042.

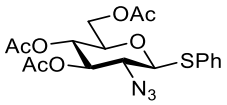
62



Following general procedure D, **57** (32 mg, 0.032 mmol), NIS (9.4 mg, 0.042 mmol), 2,6-DTBMP (13.2 mg, 0.064 mmol), and TMSOTf (7 μL, 0.039 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C for 3 h, and quenched with TBAF. The product was obtained as a white solid (20 mg, 0.024 mmol, 74%) upon flash chromatography (40 to 55% EtOAc/hex) on SiO_2. ^1H NMR (700 MHz, $CDCl_3$) δ 7.34-7.37 (m, 2H), 7.22-7.34 (m, 13H), 7.11-7.19 (m, 5H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.75-4.84 (m, 4H), 4.66 (d, *J* = 11.2 Hz, 2H), 4.61 (d, *J* = 3.5 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), **4.36 (d, *J* = 7.7 Hz, 1H)**, 4.06 (dd, *J* = 11.2, 1.4 Hz, 1H), 3.96 (t, *J* = 9.8 Hz, 1H), 3.82 (dd, *J* = 11.9, 2.1 Hz, 1H), 3.79 (t, *J* = 9.8 Hz, 1H), 3.76 (dd, *J* = 10.5, 2.1 Hz, 1H), 3.65-3.73 (m, 3H), 3.55 (t, *J* = 9.8 Hz, 1H), 3.52 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.42-3.48 (m, 2H), 3.33 (s, 3H), 3.28 (s, 3H), 3.24 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 138.8, 138.5, 138.4, 138.2, 128.4, 128.31, 128.29, 128.2, 128.1, 128.0, 127.9, 127.7, 127.62, 127.55, 127.5, 127.4, 104.0, 99.6, 99.5, 98.2, 82.0, 79.7, 78.6, 77.6, 75.7, 74.83, 74.79, 73.7, 73.4, 72.7, 69.8, 68.8, 65.9, 61.3, 55.2, 47.91, 47.90, 17.8, 17.6; IR (film, cm^{-1}) 3498, 3030,

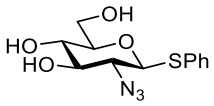
2923, 1720, 1496, 1454, 1367, 1194, 1134, 1093, 1028, 737, 697; HRMS (ES) *m/z* calcd for $C_{47}H_{58}O_{13}$ $[M+Na]^+$ 853.3770, found 853.3750.

69



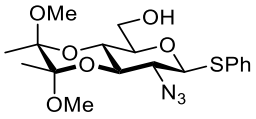
To a solution of the corresponding 2-deoxy-2-amino-thioglycoside[103] (1.03 g, 3.78 mmol), K_2CO_3 (1.04 g, 7.55 mmol), and $CuSO_4 \bullet 5H_2O$ (10 mg, 0.038 mmol) in MeOH (38 mL, 0.1 M) was added imidazole-1-sulfonyl azide (950 mg, 4.53 mmol) and the reaction was stirred overnight. The reaction was concentrated and azeotroped with toluene (x2), dissolved in pyridine (19 mL, 0.2 M), and acetic anhydride (2.8 mL, 30 mmol) was added and the reaction was stirred overnight. The reaction was diluted with ethyl acetate, washed with H_2O, washed with sat. aq. NH_4Cl (x3), dried over $MgSO_4$, filtered, and concentrated. The crude mixture was subjected to flash chromatography (20 to 30% EtOAc/hex) to give the product (376 mg, 0.888 mmol, 23%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.48-7.53 (m, 2H), 7.23-7.30 (m, 3H), 5.02 (t, *J* = 9.5 Hz, 1H), 4.84 (t, *J* = 9.5 Hz, 1H), 4.48 (d, *J* = 10.5 Hz, 1H), 4.06-4.19 (m, 2H), 3.65 (ddd, *J* = 10.0, 5.0, 2.5 Hz, 1H), 3.33 (t, *J* = 10.0 Hz, 1H), 1.99 (s, 3H), 1.97 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.3, 169.7, 169.5, 133.8, 130.3, 129.0, 128.7, 85.4, 75.5, 74.2, 68.0, 62.5, 61.9, 20.6, 20.5, 20.4; IR (film, cm^{-1}) 2110, 1744, 1439, 1365, 1221, 1047; HRMS (ES) *m/z* calcd for $C_{18}H_{21}N_3O_7S$ $[M+NH_4]^+$ 441.1438, found 441.1439.

70



To a solution of **69** (376 mg, 0.89 mmol) in methanol (9 mL, 0.1 M) was added NaOMe (5 mg, 0.089 mmol) and the reaction was stirred overnight. The reaction was concentrated to give the product (256 mg, 0.86 mmol, 97%) without further purification as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.55-7.61 (m, 2H), 7.26-7.36 (m, 3H), 4.54 (d, *J* = 10.0 Hz, 1H), 3.86 (dd, *J* = 12.0, 1.6 Hz, 1H), 3.65-3.72 (m, 1H), 3.38-3.45 (m, 1H), 3.26-3.36 (m, 1H), 3.14 (t, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 136.4, 136.2, 132.6, 131.6, 89.8, 84.7, 81.0, 73.7, 69.6, 65.2; IR (film, cm^{-1}) 3344, 2918, 2110, 1584, 1439, 1352, 1273, 1068, 1024; HRMS (ES) *m/z* calcd for $C_{12}H_{15}N_3O_4S$ $[M+Cl]^-$ 332.0477, found 332.0473.

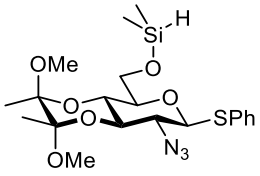
71



To a solution of **70** (256 mg, 0.86 mmol), 2,3-butadione (83 μL, 0.95 mmol), and $CH(OCH_3)_3$ (310 μL, 2.84 mmol) in methanol (9 mL, 0.1 M) was added camphorsulfonic acid (40 mg, 0.17 mmol) and the reaction was refluxed overnight, quenched with NEt_3, and concentrated. The crude mixture was subjected to flash chromatography (15 to 18% EtOAc/hex) and recrystallized (H_2O/EtOH) to give the product (204 mg, 0.50 mmol, 58%) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.31-7.38 (m, 2H), 7.10-7.17 (m, 3H), 4.25 (d, *J* = 9.6 Hz, 1H), 3.68 (d, *J* = 12.0 Hz, 1H), 3.47-3.58 (m, 2H), 3.44 (t, *J* = 9.6 Hz, 1H), 3.32 (ddd, *J* = 9.6, 4.8, 2.4 Hz, 1H), 3.20 (t, *J* = 10.0 Hz, 1H), 3.12 (s, 3H), 3.04 (s, 3H), 1.90 (s, 1H), 1.13 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

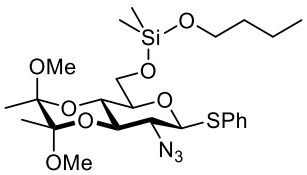
133.7, 130.7, 129.1, 128.6, 100.2, 99.7, 86.1, 78.1, 72.9, 65.6, 61.4, 61.2, 48.0, 17.6, 17.5; IR (film, cm^{-1}) 3500, 2992, 2948, 2833, 2223, 2108, 1582, 1474, 1439, 1368, 1322, 1277, 1220, 1113, 1048, 1030; HRMS (ES) *m/z* calcd for $C_{18}H_{25}N_3O_6S$ $[M+NH_4]^+$ 429.1802, found 429.1800.

72



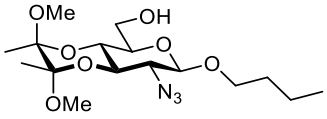
Following general procedure A, **71** (204 mg, 0.5 mmol), NEt_3 (138 μL, 0.99 mmol), and Me_2SiHCl (83 μL, 0.74 mmol) were stirred at 0 °C for 5 h. The product (222 mg, 0.47 mmol, 95%) was obtained as a white solid after aqueous workup. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.62 (m, 2H), 7.24-7.34 (m, 3H), 4.66 (quin, *J* = 2.8 Hz, 1H), 4.37 (d, *J* = 9.6 Hz, 1H), 3.77-3.92 (m, 2H), 3.63-3.76 (m, 2H), 3.42-3.50 (m, 1H), 3.71 (t, *J* = 9.6 Hz, 1H), 3.30 (s, 3H), 3.23 (s, 3H), 1.30 (s, 3H), 1.25 (s, 3H), 0.20 (t, *J* = 2.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 134.0, 130.9, 128.9, 128.4, 100.1, 99.7, 86.0, 78.5, 73.1, 65.0, 62.2, 61.3, 48.0, 17.6, 17.5, -1.40, -1.44; IR (film, cm^{-1}) 2943, 2837, 2110, 1438, 1375, 1366, 1274, 1250, 1111, 1030, 896; HRMS (ES) *m/z* calcd for $C_{20}H_{31}N_3O_6SSi$ $[M+NH_4]^+$ 487.2041, found 487.2035.

73



Following general procedure C, **72** (52 mg, 0.11 mmol), butanol (9.2 μL, 0.1 mmol), CuCl•IPr (2.5 mg, 0.005 mmol), NaOtBu (0.48 mg, 0.005 mmol), and 4Å molecular sieves (40 mg) were stirred overnight. The product (46 mg, 0.085 mmol, 85%) was obtained as a white solid upon flash chromatography (5 to 15% EtOAc/hex) on SiO_2. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55-7.60 (m, 2H), 7.26-7.32 (m, 3H), 4.39 (d, *J* = 9.8 Hz, 1H), 3.94 (dd, *J* = 11.9, 1.4 Hz, 1H), 3.84 (dd, *J* = 11.2, 4.2 Hz, 1H), 3.68-3.74 (m, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 3.44-3.48 (m, 1H), 3.92 (t, *J* = 9.8 Hz, 1H), 3.31 (s, 3H), 3.24 (s, 3H), 1.51 (quin, *J* = 7.0 Hz, 2H), 1.29-1.36 (m, 2H), 1.31 (s, 3H), 1.26 (s, 3H), 0.88 (t, *J* = 7.7 Hz, 3H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 133.6, 131.3, 128.9, 128.3, 100.2, 99.7, 86.1, 78.5, 73.2, 65.3, 62.0, 61.4, 60.5, 48.0, 48.0, 34.7, 18.9, 17.6, 17.5, 13.8, -3.0, -3.2; IR (film, cm^{-1}) 2956, 2930, 2109, 1454, 1439, 1375, 1367, 1288, 1256, 1111, 1092, 1067, 1030, 848; HRMS (ES) *m/z* calcd for $C_{24}H_{39}N_3O_7SSi$ $[M+NH_4]^+$ 559.2616, found 559.2620.

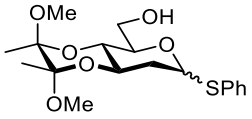
74



Following general procedure D, **73** (44 mg, 0.081 mmol), NIS (24 mg, 0.106 mmol), 2,6-DTBMP (33 mg, 0.162 mmol), and TMSOTf (18 μL, 0.097 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C for 1 h, and quenched with TBAF. The product (24 mg, 0.064 mmol, 80%) was obtained as a white solid upon flash chromatography (25 to 35% EtOAc/hex) on SiO_2. ^{1}H (700 MHz, $CDCl_3$) δ **4.26 (d, *J* = 8.4 Hz, 1H)**, 3.84 (dt, *J* = 9.8, 6.3 Hz, 1H), 3.79 (d, *J* = 11.9 Hz, 1H), 3.63-3.70 (m, 2H), 3.52 (t, *J* = 9.8 Hz, 1H), 3.48 (dt, *J* = 9.1, 7.0 Hz, 1H), 3.39-3.42 (m, 1H), 3.35 (dd, *J* = 10.5, 7.7 Hz, 1H), 3.24 (s, 3H),

3.19 (s, 3H), 1.84 (s, 1H), 1.51-1.61 (m, 2H), 1.29-1.40 (m, 2H), 1.28 (s, 3H), 1.22 (s, 3H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 102.7, 100.0, 99.7, 73.9, 70.6, 70.4, 66.0, 62.8, 61.1, 48.0, 48.0, 31.5, 19.1, 17.6, 17.5, 13.8; IR (film, cm^{-1}) 3501, 2956, 2874, 2108, 1460, 1371, 1279, 1262, 1222, 1202, 1117, 1099, 1065, 1029; HRMS (ES) *m/z* calcd for $C_{16}H_{29}N_3O_7$ $[M+Na]^+$ 398.1898, found 398.1899.

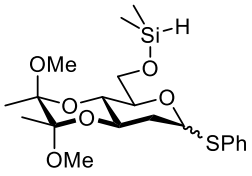
76



To a solution of 2-deoxy-thioglycoside[104] (2.23 g, 8.7 mmol), 2,3-butadione (840 μL, 9.6 mmol), and $CH(OCH_3)_3$ (3.2 mL, 28.7 mmol) in methanol (87 mL, 0.1 M) was added camphorsulfonic acid (400 mg, 1.7 mmol) and the reaction was refluxed overnight, quenched with NEt_3, and concentrated. The crude mixture was subjected to flash chromatography (5 to 35% EtOAc/hex) to give the product (2.26 g, 6.1 mmol, 70%) as a colorless foam. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.44-7.49 (m, 3.1H), 7.25-7.33 (m, 4.7H), 5.64-5.67 (m, 1H, *α*-anomer), 4.88 (dd, J = 11.2, 1.4 Hz,, 0.56H, *β*-anomer), 4.27 (td, J = 11.2, 1.4 Hz, 1H, *α*-anomer), 4.13-4.19 (m, 1.2H), 3.83-3.90 (m, 1.2H), 3.72-3.82 (m, 2.8H), 3.66 (t, J = 10.5 Hz, 1H, *α*-anomer), 3.58 (t, J = 9.8 Hz, 0.56H, *β*-anomer), 3.52 (ddd, J = 9.8, 4.9, 2.8 Hz, 0.56H, *β*-anomer), 3.33 (s, 3H, *α*-anomer), 3.28 (s, 3H, *α*-anomer), 3.27 (s, 1.7H, *β*-anomer), 3.25 (s, 1.7H, *β*-anomer), 2.20-3.23 (m, 2H, *α*-anomer), 2.18 (ddd, J = 12.6, 4.2, 2.1 Hz, 0.56H, *β*-anomer), 1.96 (dd, J = 7.0, 5.6 Hz, 0.56H, *β*-anomer), 1.86 (q, J = 11.9 Hz, 0.56H, *β*-anomer), 1.69 (dd, J = 7.7, 5.6 Hz, 1H, *α*-anomer), 1.33 (s, 3H, *α*-anomer), 1.32 (s, 3H, *α*-anomer), 1.30 (s, 1.7H, *β*-anomer), 1.29 (s, 1.7H, *β*-anomer); ^{13}C NMR (175 MHz, $CDCl_3$) δ 134.4, 133.0, 131.93, 131.91,

129.0, 127.8, 127.5, 100.0, 99.91, 99.89, 84.3, 82.5, 77.9, 70.9, 68.8, 68.4, 68.0, 65.6, 61.7, 61.3, 48.1, 48.0, 47.92, 47.91, 36.0, 35.3, 17.8, 17.74, 17.69; IR (film, cm^{-1}) 3500, 2944, 2354, 1457, 1379, 1126, 1048, 918, 739, 678; HRMS (ES) *m/z* calcd for $C_{18}H_{26}O_6S$ $[M+Na]^+$ 393.1342, found 393.1347.

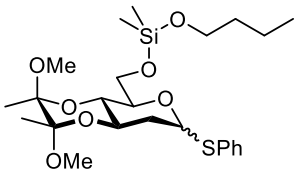
77



Following general procedure A, **76** (2.26 mg, 6.1 mmol), NEt_3 (1.7 mL, 12.2 mmol), and Me_2SiHCl (1.02 mL, 9.2 mmol) were stirred at 0 °C for 4 h. The product (2.48 g, 5.8 mmol, 95%) was obtained as a purple oil after aqueous workup. ^1H NMR (700 MHz, $CDCl_3$) δ 7.51-7.53 (m, 1.0H), 7.44-7.47 (m, 1.9H), 7.24-7.29 (m, 3.9H), 7.21-7.24 (m, 1.0H), 5.68 (d, *J* = 4.9 Hz, 1H, *α*-anomer), 4.81 (dd, *J* = 11.2, 2.1 Hz, 0.56H, *β*-anomer), 4.66 (quin, *J* = 2.8 Hz, 0.56H, *β*-anomer), 4.60 (quin, *J* = 2.8 Hz, 1H, *α*-anomer), 4.23 (ddd, *J* = 9.8, 4.2, 1.4 Hz, 1H, *α*-anomer), 4.12 (ddd, *J* = 11.9, 9.8, 4.9 Hz, 1H, *α*-anomer), 3.90 (d, *J* = 4.2 Hz, 0.56H, *β*-anomer), 3.89 (d, *J* = 5.6 Hz, 1H, *α*-anomer), 3.80-3.86 (m, 1.2H), 3.78 (dd, *J* = 11.2, 2.1 Hz, 1H, *α*-anomer), 3.70 (t, *J* = 9.8 Hz, 1H, *α*-anomer), 3.58 (t, *J* = 9.8 Hz, 0.56H, *β*-anomer), 3.45 (ddd, *J* = 9.8, 4.9, 2.1 Hz, 0.56H, *β*-anomer), 3.31 (s, 3H, *α*-anomer), 3.28 (s, 3H, *α*-anomer), 3.25 (s, 1.7H, *β*-anomer), 3.25 (s, 1.7H, *β*-anomer), 2.15-2.24 (m, 2H, *α*-anomer), 2.13 (ddd, *J* = 11.9, 4.2, 2.1 Hz, 0.56H, *β*-anomer), 1.84 (q, *J* = 11.9 Hz, 0.56H, *β*-anomer), 1.32 (s, 3H, *α*-anomer), 1.31 (s, 3H, *α*-anomer), 1.281 (s, 1.7H, *β*-anomer), 1.275 (s, 1.7H, *β*-anomer), 0.21 (d, *J* = 2.1 Hz, 1.7H, *β*-anomer), 0.20 (d, *J* = 2.8 Hz, 1.7H, *β*-anomer), 0.17 (d, *J* = 2.8 Hz, 1.7H, *β*-

anomer); ^{13}C (175 MHz, $CDCl_3$) δ 135.1, 133.6, 132.1, 131.3, 128.81, 128.75, 127.5, 127.1, 99.9, 99.8, 84.3, 82.4, 78.6, 71.4, 68.7, 68.2, 67.4, 65.8, 62.8, 62.3, 48.03, 47.98, 47.9, 36.0, 35.5, 17.81, 17.78, 17.75, 17.7, -1.29, -1.34, -1.5, -1.6; IR (film, cm^{-1}) 2947, 2354, 2120, 1455, 1378, 1248, 1120, 1054, 897, 747, 685; HRMS (ES) *m/z* calcd for $C_{20}H_{32}O_6SSi$ $[M+Na]^+$ 451.1581, found 451.1583.

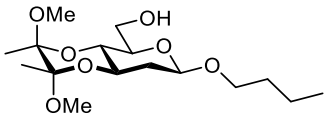
78



Following general procedure C, **77** (47 mg, 0.11 mmol), butanol (9.2 μL, 0.1 mmol), CuCl•IPr (2.5 mg, 0.005 mmol), NaOtBu (0.48 mg, 0.005 mmol), and 4Å molecular sieves (40 mg) were stirred overnight. The product (44 mg, 0.088 mmol, 88%) was obtained as a white solid upon flash chromatography (5 to 15% EtOAc/hex) on SiO_2. ^1H NMR (700 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.0 Hz, 1.1H, *β*-anomer), 7.45 (d, *J* = 7.7 Hz, 2H, *α*-anomer), 7.19-7.28 (m, 4.6H), 5.65 (d, *J* = 4.9 Hz, 1H, *α*-anomer), 4.82 (dd, *J* = 11.2, 1.4 Hz, 0.54H, *β*-anomer), 4.23 (dt, *J* = 9.8, 2.1 Hz, 1H, *α*-anomer), 4.12 (dt, *J* = 10.5, 5.6 Hz, 1H, *α*-anomer), 3.96 (d, *J* = 4.9 Hz, 0.54H, *β*-anomer), 3.80-3.92 (m, 3.2H), 3.64-3.70 (m, 2H), 3.62 (*t*, *J* = 7.0 Hz, 1H, *α*-anomer), 3.60 (t, *J* = 9.1 Hz, 0.54H, *β*-anomer), 3.45 (ddd, *J* = 9.8, 4.2, 1.4 Hz, 0.54H, *α*-anomer), 3.31 (s, 3H), 3.27 (s, 3H), 3.25 (s, 3H), 2.15-2.23 (m, 2H, *α*-anomer), 2.13 (ddd, *J* = 12.6, 4.2, 1.4 Hz, 0.54H, *β*-anomer), 1.84 (q, *J* = 11.9 Hz, 0.54H, *β*-anomer), 1.46-1.53 (m, 3.1H), 1.28-1.35 (m, 3.1H), 1.31 (s, 3H, *α*-anomer), 1.30 (s, 3H, *α*-anomer), 1.28 (s, 1.6H, *β*-anomer), 1.27 (s, 1.6H, *β*-anomer), 0.88 (t, *J* = 7.0 Hz, 4.6H), 0.123 (s, 1.6H, *β*-anomer), 0.118 (s, 1.6H, *β*-anomer), 0.08 (s, 6H,

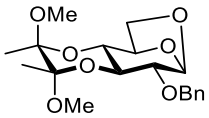
α-anomer); ^{13}C NMR (175 MHz, $CDCl_3$) δ 135.1, 133.9, 131.7, 131.4, 128.8, 128.7, 127.3, 127.0, 99.9, 99.84, 99.82, 84.3, 82.4, 78.6, 71.4, 68.7, 68.3, 67.4, 65.8, 62.3, 61.1, 60.7, 48.0, 48.0, 47.92, 47.89, 36.0, 35.5, 34.7, 34.6, 18.9, 17.81, 17.76, 17.7, 13.8, -3.0, -3.10, -3.14, -3.3; IR (film, cm^{-1}) 2956, 1584, 1456, 1376, 1255, 1114, 1074, 1051, 1037, 976, 926, 882, 848, 797, 740, 691, 642; HRMS (ES) *m/z* calcd for $C_{24}H_{40}O_7SSi$ $[M+NH_4]^+$ 518.2602, 518.2602.

79



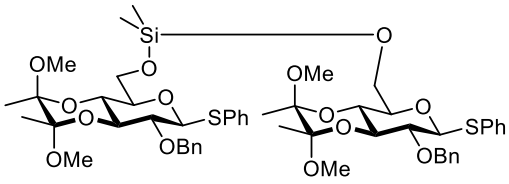
Following general procedure D, **78** (32 mg, 0.064 mmol), NIS (19 mg, 0.083 mmol), 2,6-DTBMP (26 mg, 0.128 mmol), and TMSOTf (14 μL, 0.077 mmol) were stirred at -78 °C for 1 h and quenched with TBAF. The product (16 mg, 0.048 mmol, 90%) was obtained as a white solid upon flash chromatography (25 to 35% EtOAc/hex) on SiO_2. ^{1}H (700 MHz, $CDCl_3$) δ **4.57 (dd, *J* = 9.8, 1.4 Hz, 1H)**, 3.82-3.88 (m, 2H), 3.78 (ddd, *J* = 12.6, 9.8, 4.2 Hz, 1H), 3.71-3.76 (m, 1H), 3.57 (t, *J* = 9.8 Hz, 1H), 3.42-3.48 (m, 2H), 3.26 (s, 3H), 3.24 (s, 3H), 2.04 (ddd, *J* = 12.6, 4.2, 2.1 Hz, 1H), 1.20 (s, 1H), 1.69 (td, *J* = 12.6, 9.8 Hz, 1H), 1.56 (quin, *J* = 7.0 Hz, 2H), 1.35 (sept, *J* = 7.0 Hz, 2H), 1.29 (s, 3H), 1.28 (s, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C (175 MHz, $CDCl_3$) 100.7, 99.80, 99.78, 73.9, 69.5, 68.3, 67.6, 61.6, 48.0, 47.9, 35.9, 31.6, 19.2, 17.8, 17.7, 13.8; IR (film, cm^{-1}) 3472, 2957, 1456, 1373, 1118, 1092, 1050, 1035, 926, 885, 846; HRMS (ES) *m/z* calcd for $C_{16}H_{30}O_7$ $[M+Na]^+$ 357.1884, found 357.1882.

1,6-Anhydro Product



The 1,6-anhydro byproduct was synthesized for spectral comparison. Following the general procedure, **45** (45 mg, 0.094 mmol), NIS (28 mg, 0.123 mmol), 2,6-DTBMP (58 mg, 0.283 mmol), and TMSOTf (38 μL, 0.208 mmol) were stirred at -40 °C for 10 min, warmed to 0 °C for 2 h, and quenched with TBAF. The product (18 mg, 0.049 mmol, 51%) was obtained as a white solid upon flash chromatography (5 to 15% EtOAc/hex) on SiO_2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.38 (m, 4H), 7.24-7.30 (m, 1H), **5.35 (s, 1H)**, 4.79 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 2.1 Hz, 1H), 3.94 (t, *J* = 12.6 Hz, 1H), 3.62-3.70 (m, 2H), 3.51 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.36 (d, *J* = 11.2 Hz, 1H), 3.31 (s, 3H), 3.24 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 128.3, 127.6, 127.5, 103.3, 100.4, 100.1, 80.4, 75.2, 72.6, 70.6, 70.2, 70.1, 47.91, 47.86, 17.9, 17.8; IR (film, cm^{-1}) 2991, 2950, 2902, 1497, 1454, 1375, 1210, 1134, 1112, 1076, 1051, 1036; HRMS (ES) *m/z* calcd for $C_{19}H_{26}O_7$ $[M+NH_4]^+$ 389.1571, 389.1571.

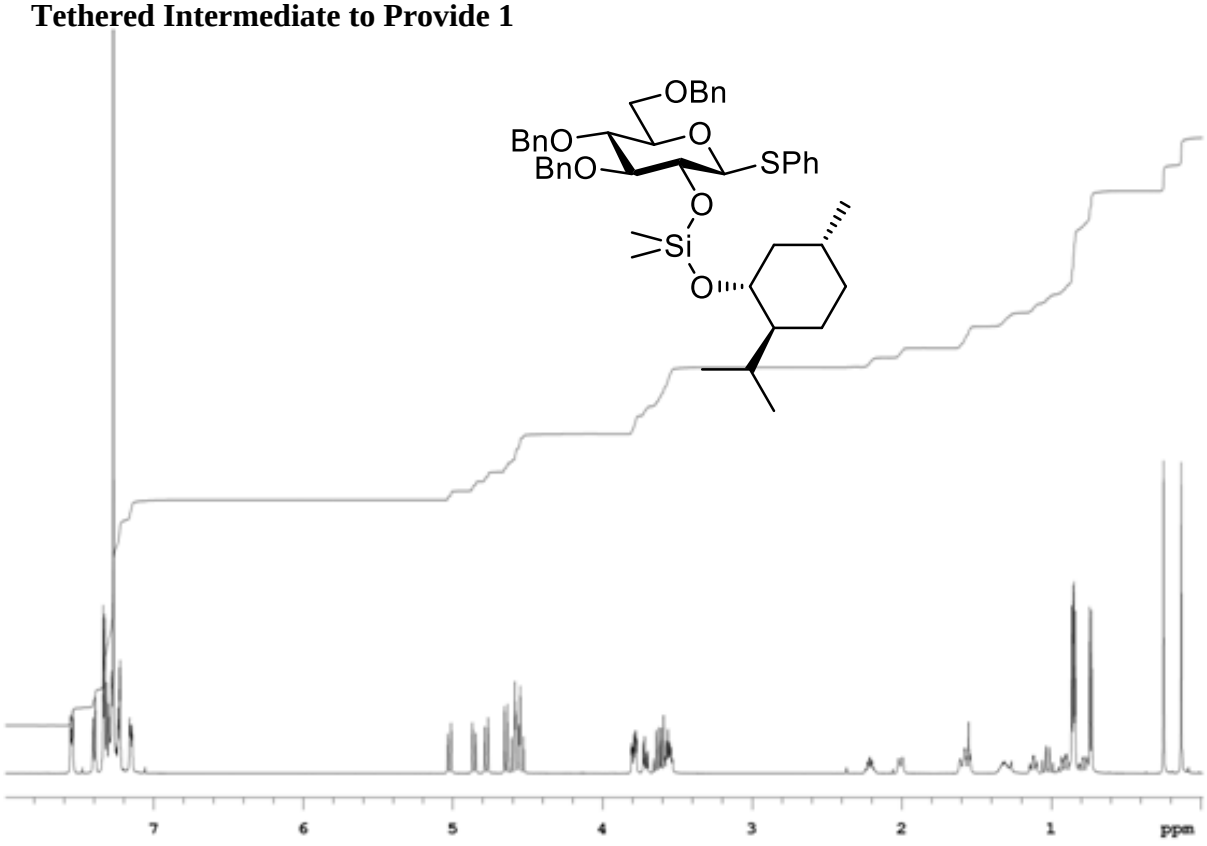
Homodimer

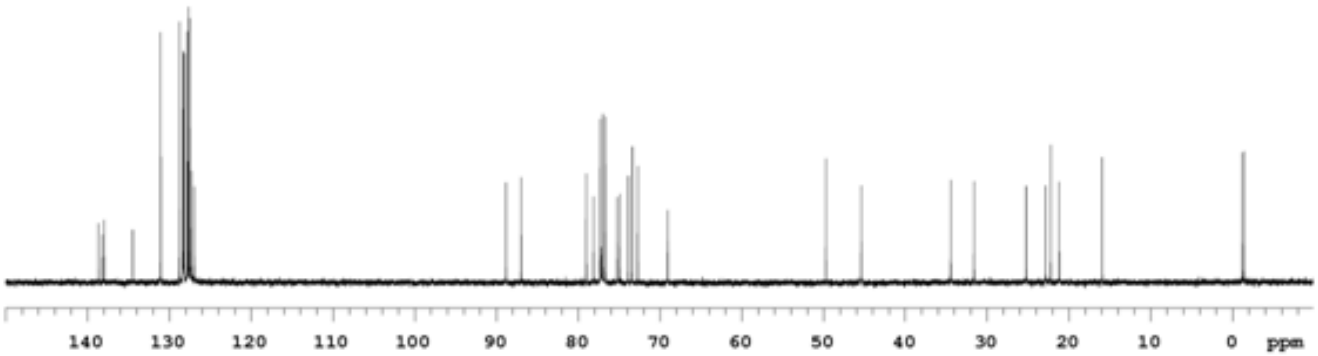


The bis-dimer was synthesized for spectral comparison. Following the general procedure, **46** (51 mg, 0.095 mmol), **45** (41 mg, 0.086 mmol), CuCl•IPr (2.4 mg, 0.005 mmol), NaOtBu (0.48 mg, 0.005 mmol), and 4Å molecular sieves (40 mg) were stirred overnight. The product (63 mg, 0.062 mmol, 72%) was obtained as a white solid upon flash chromatography (5 to 15% EtOAc/hex) on SiO_2. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53-7.57

(m, 4H), 7.40-7.44 (m, 4H), 7.33 (t, *J* = 7.0 Hz, 4H), 7.21-7.31 (m, 8H), 4.80 (d, *J* = 10.5 Hz, 2H), 4.71 (d, *J* = 10.5 Hz, 2H), 4.63 (d, *J* = 9.8 Hz, 2H), 4.00 (dd, *J* = 11.2, 1.4 Hz, 2H), 3.82-3.90 (m, 4H), 3.74 (t, *J* = 9.8 Hz, 2H), 3.44-3.49 (m, 4H), 3.26 (s, 6H), 3.24 (s, 6H), 1.33 (s, 6H), 1.27 (s, 6H), 0.16 (s, 6H); ^{13}C NMR (175 MHz, $CDCl_3$) 138.4, 133.5, 132.3, 128.8, 128.3, 128.2, 127.7, 127.4, 99.6, 99.5, 87.3, 78.2, 77.5, 75.4, 74.8, 65.2, 60.8, 48.0, 47.9, 17.8, 17.6, -3.0; HRMS (ES) *m/z* calcd for $C_{52}H_{68}O_{14}S_2Si$ $[M+NH_4]^+$ 1026.4158, found 1026.4155.

Tethered Intermediate to Provide 1





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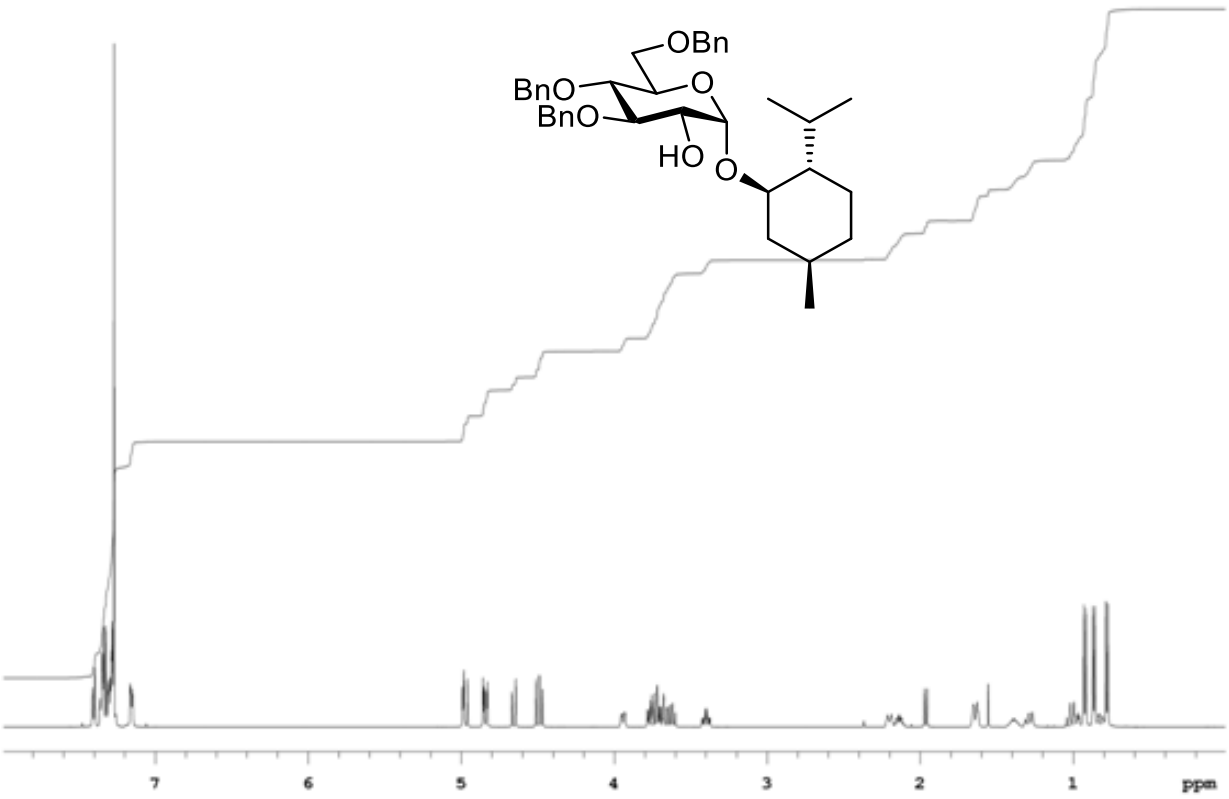
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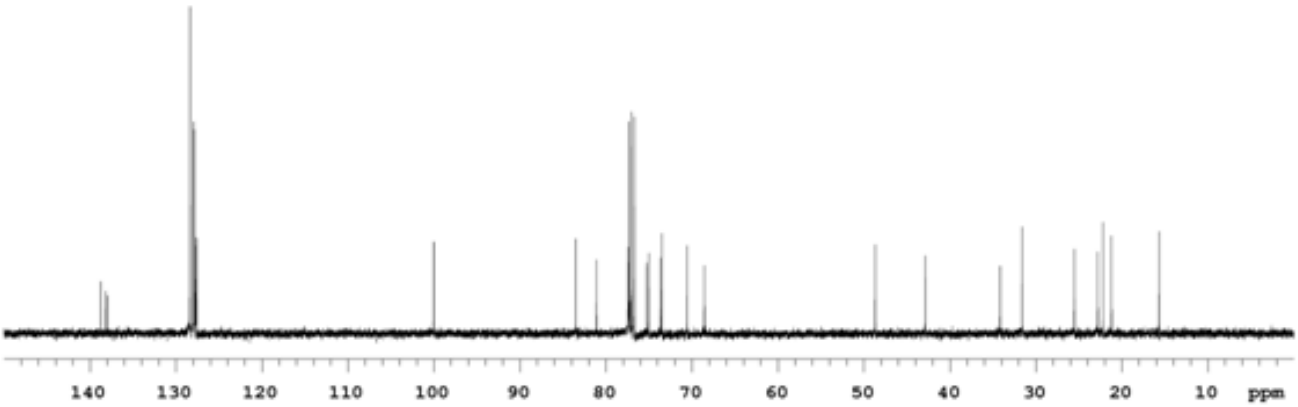
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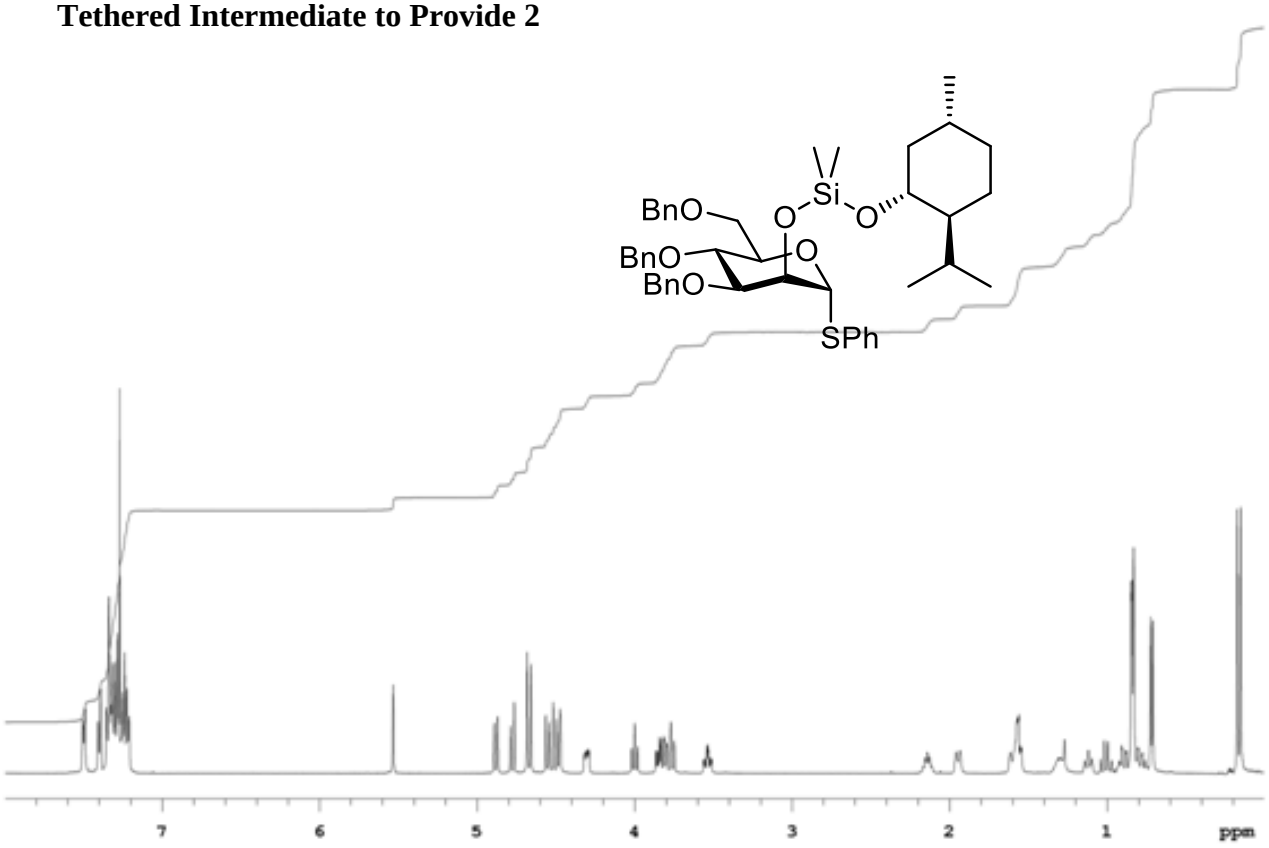

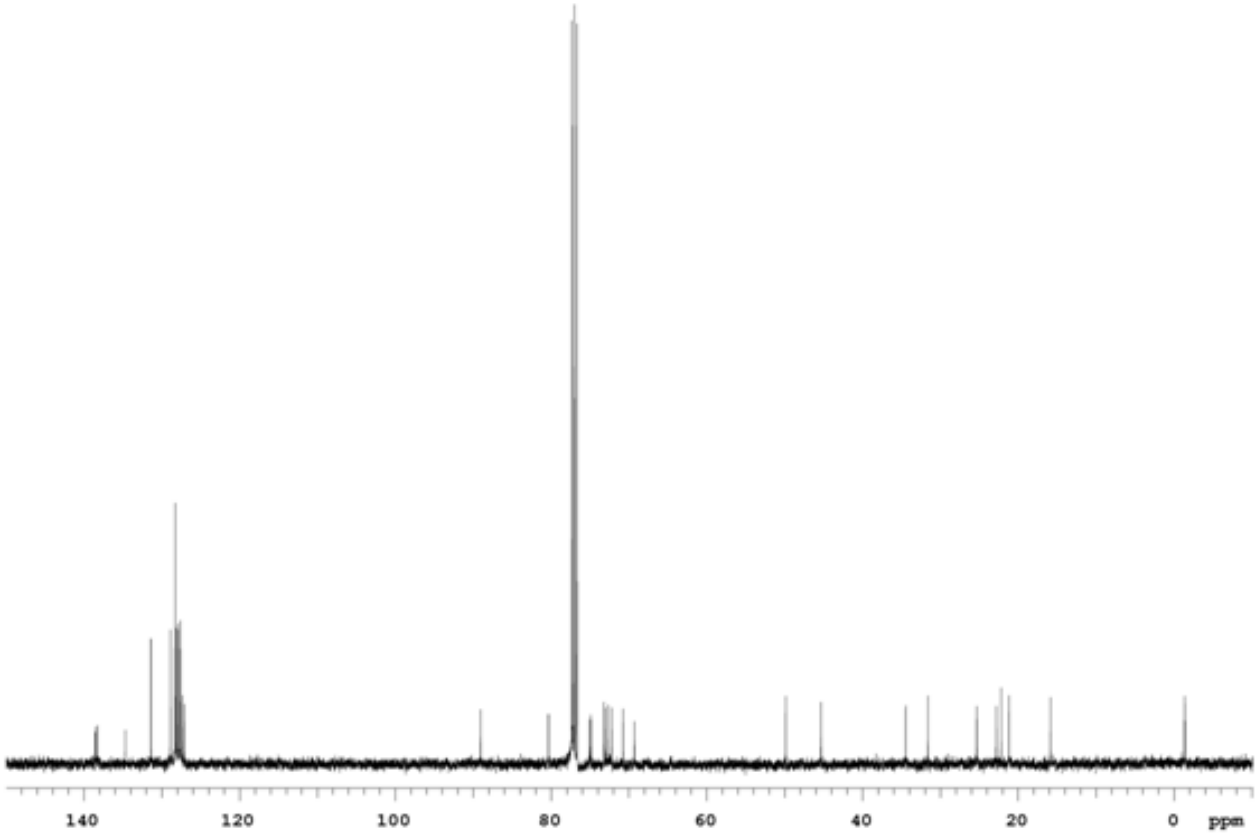

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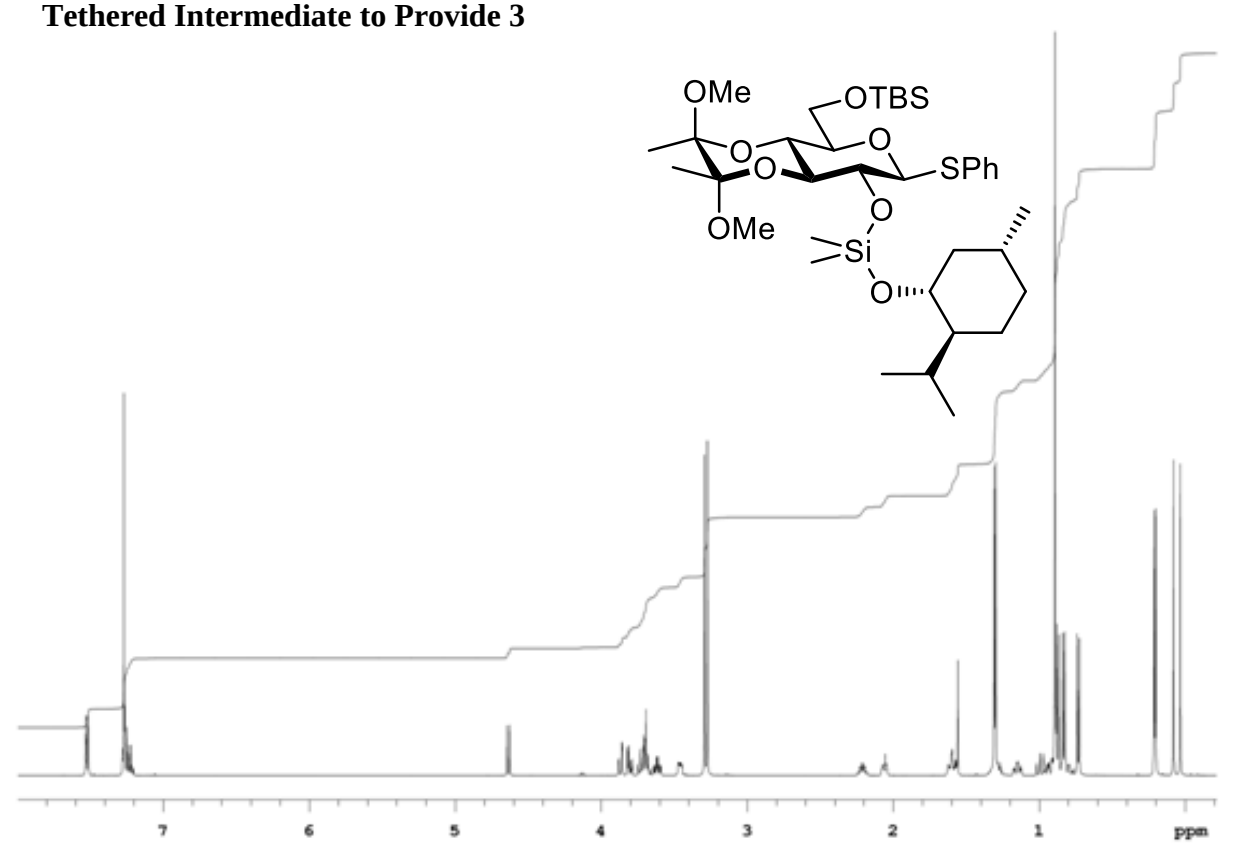

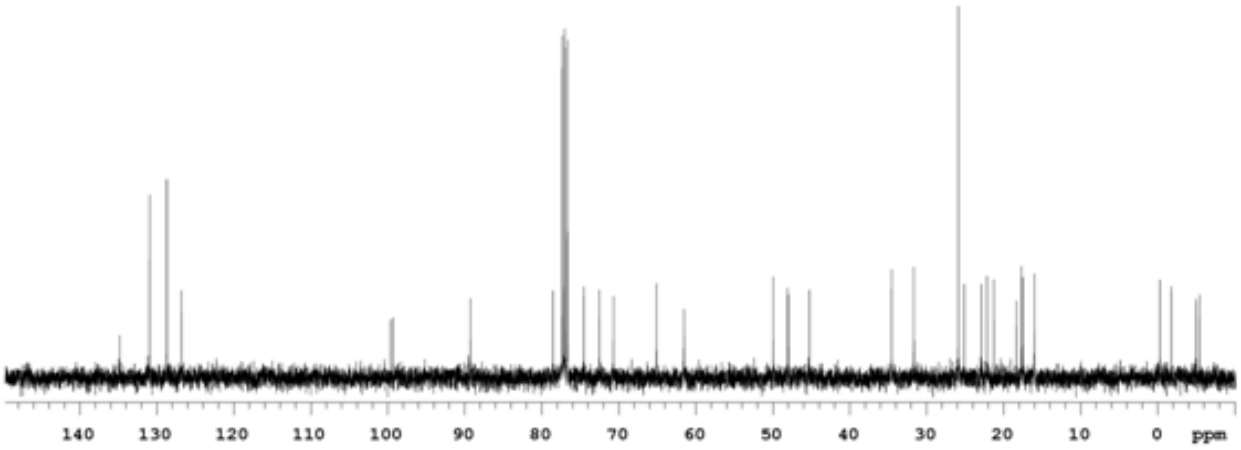

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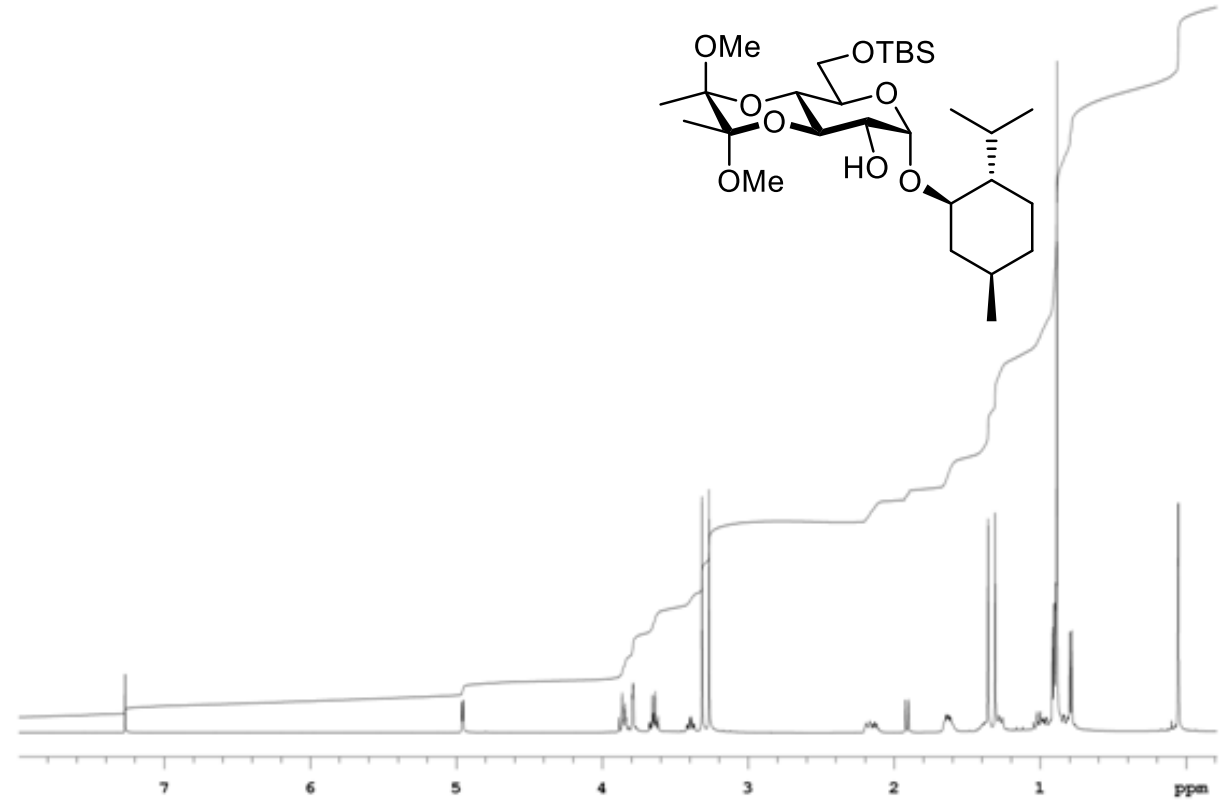

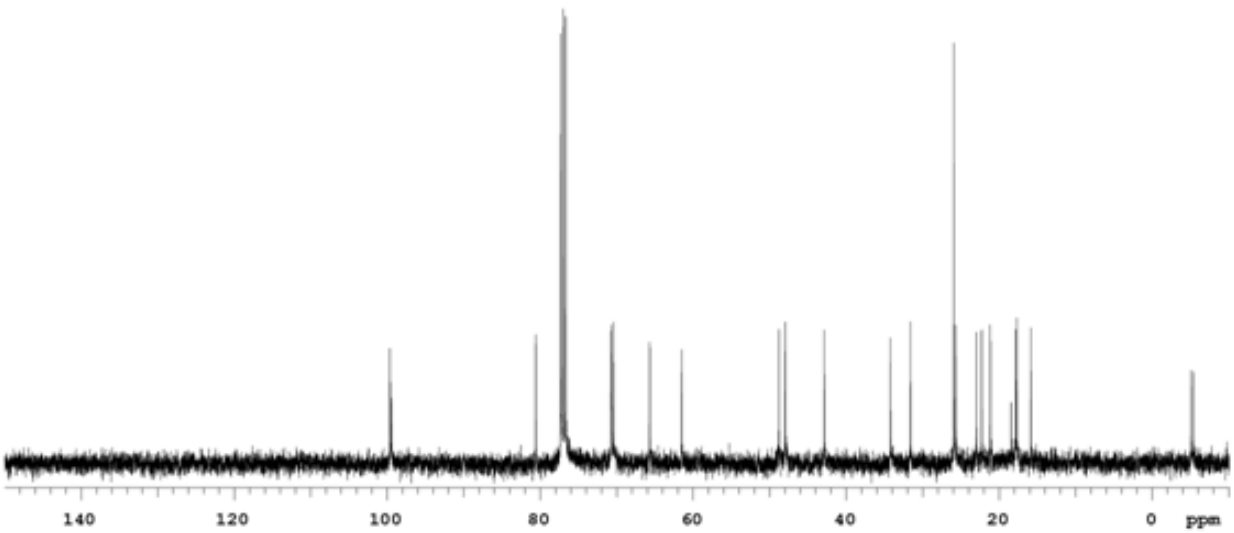

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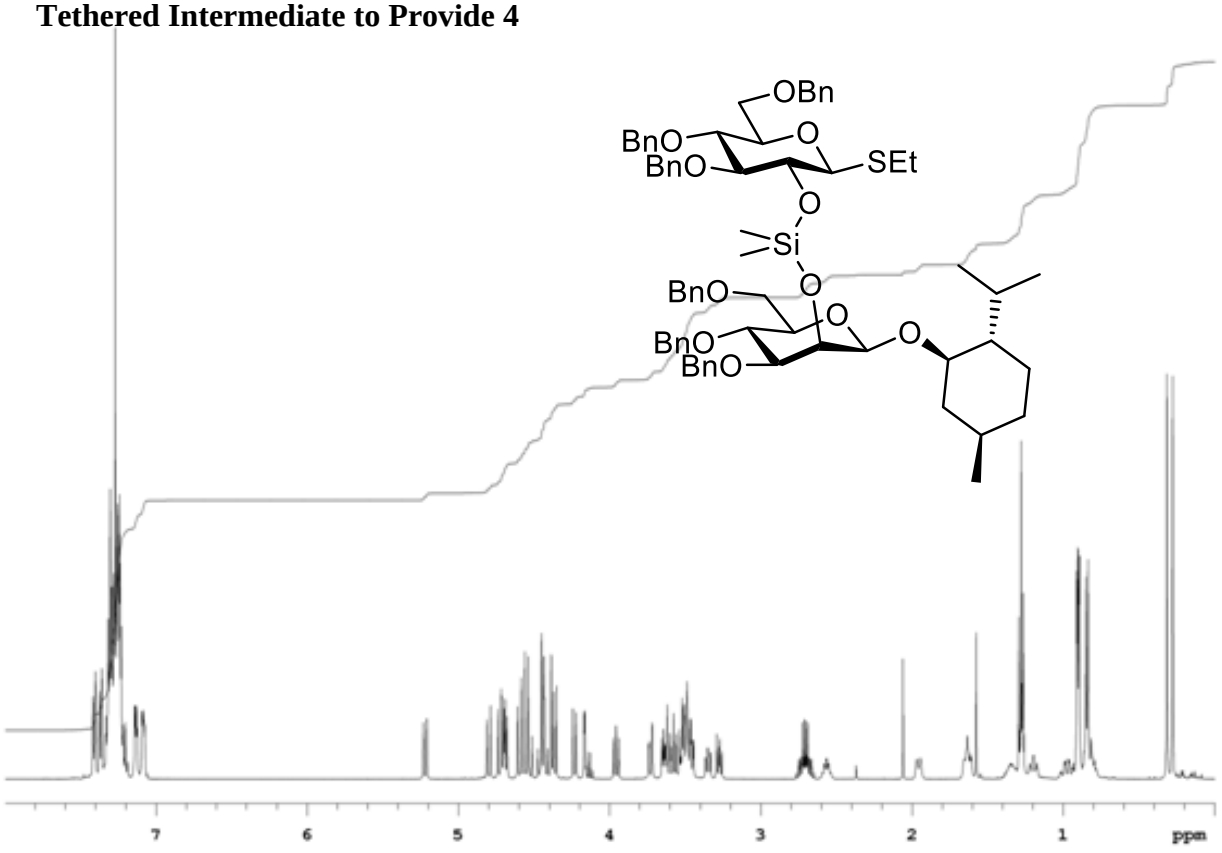

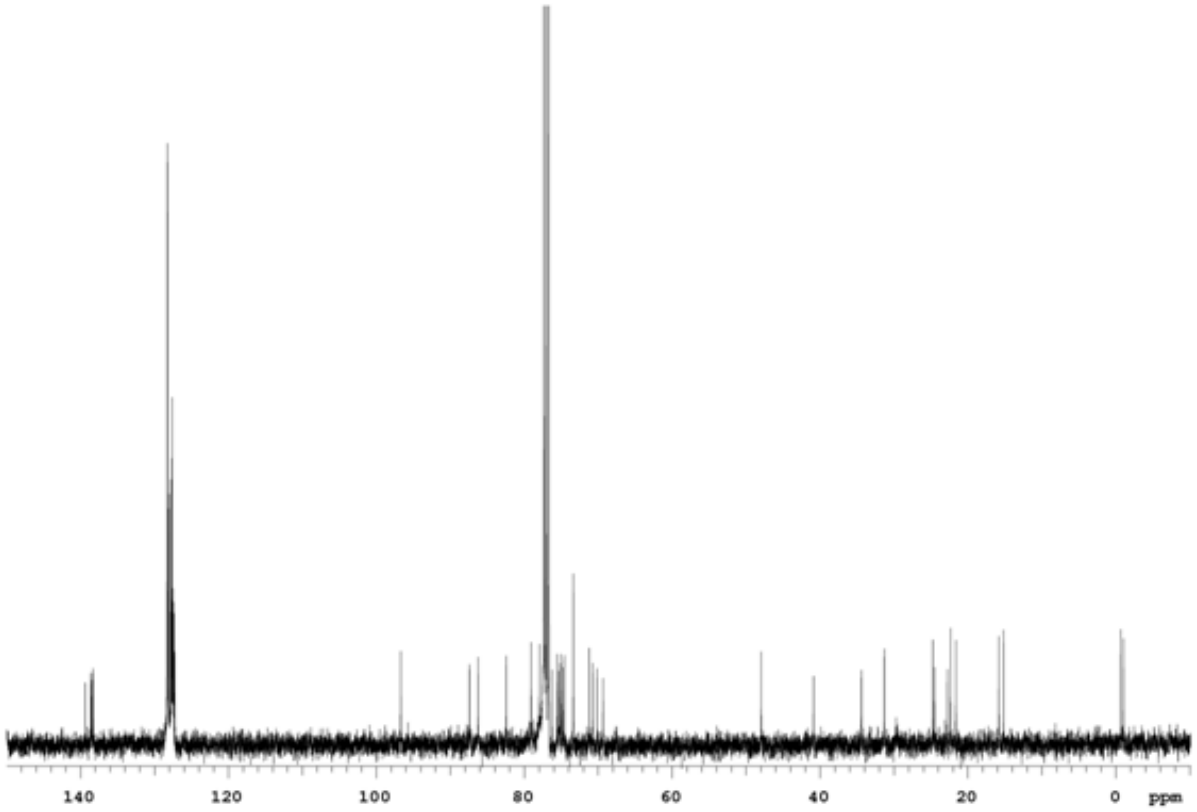

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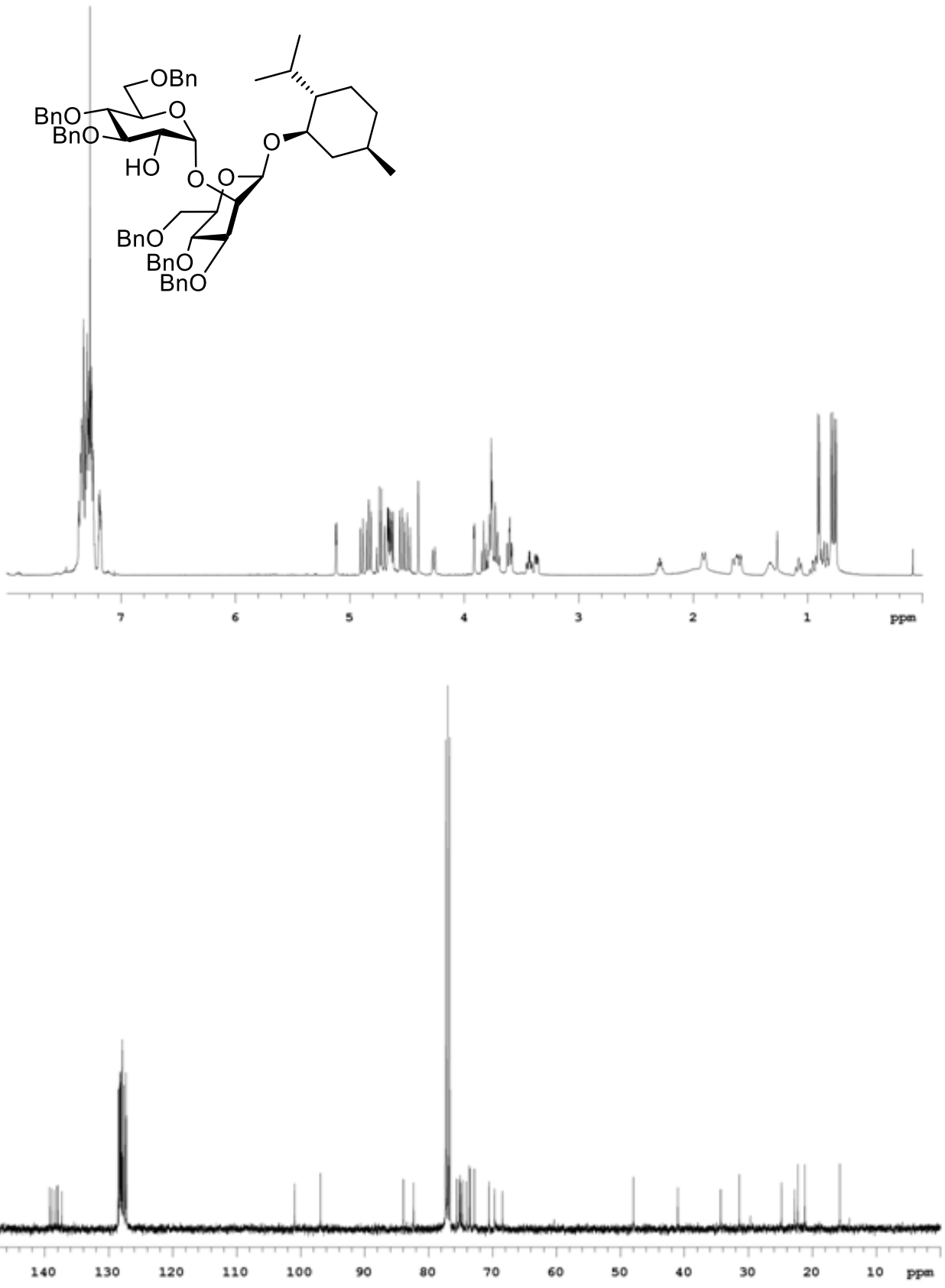
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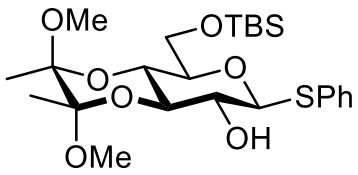
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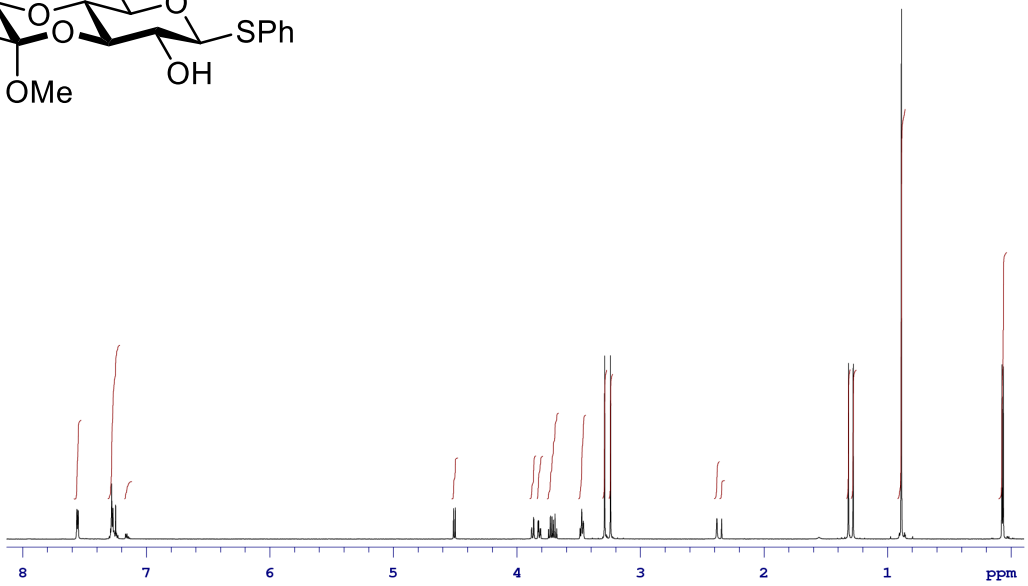
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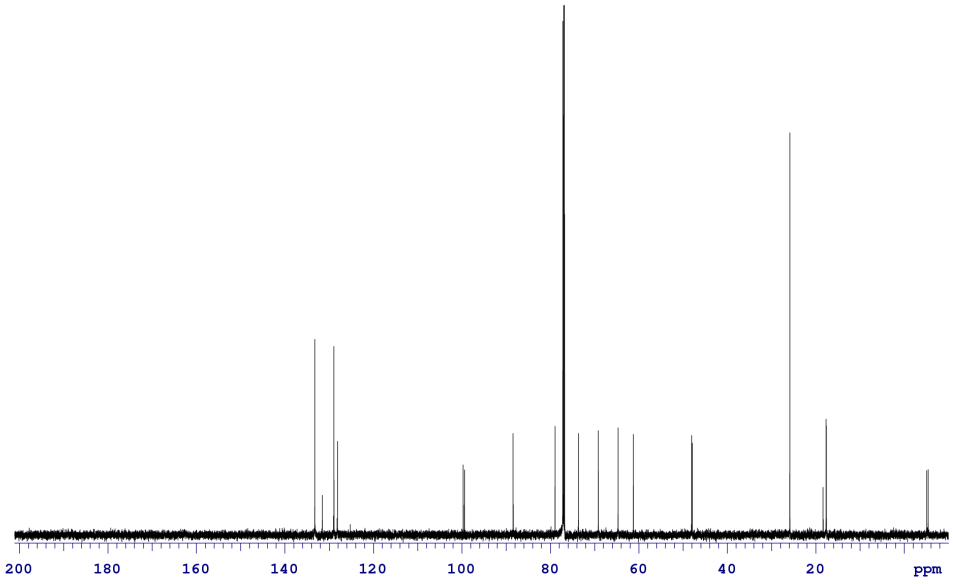
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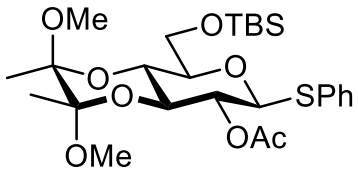
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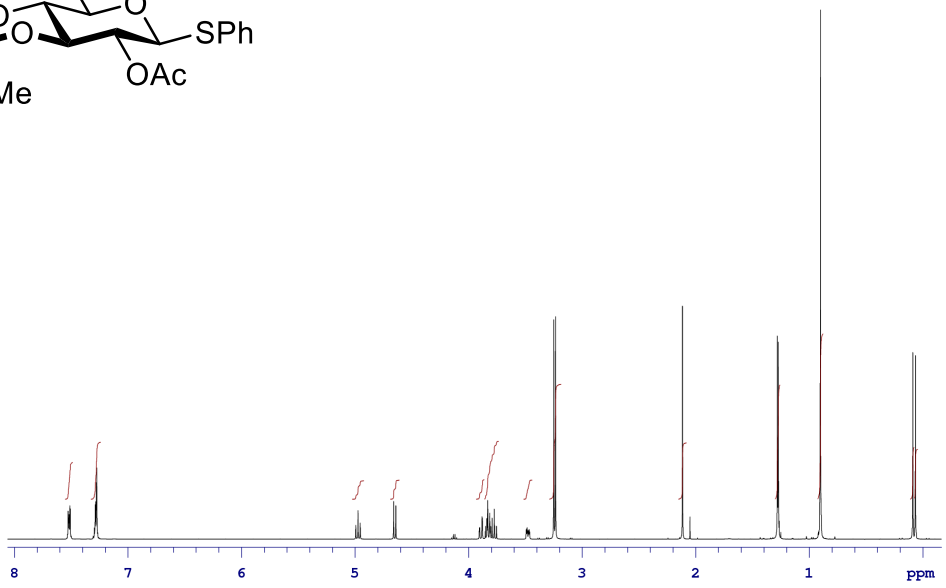
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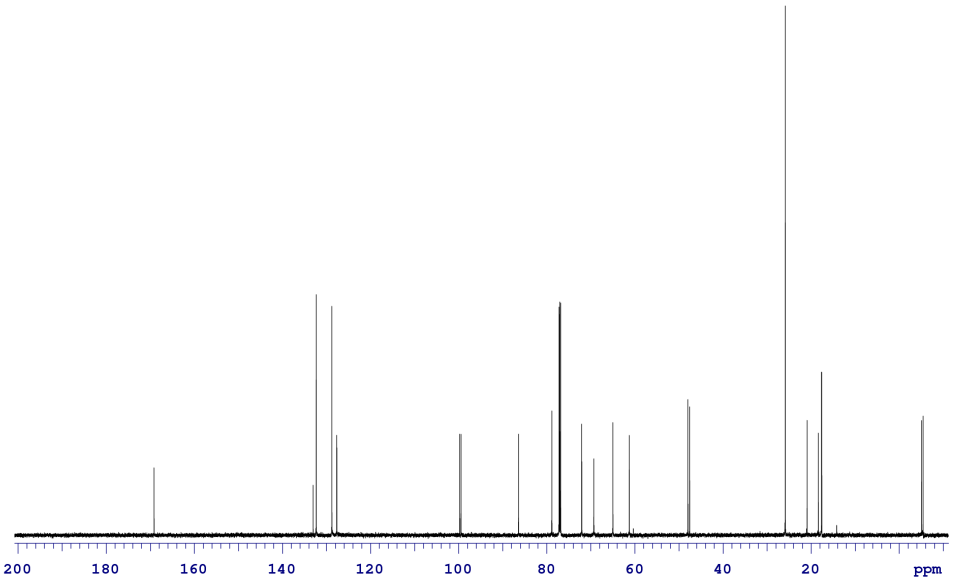
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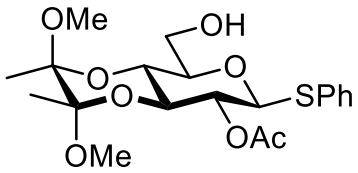
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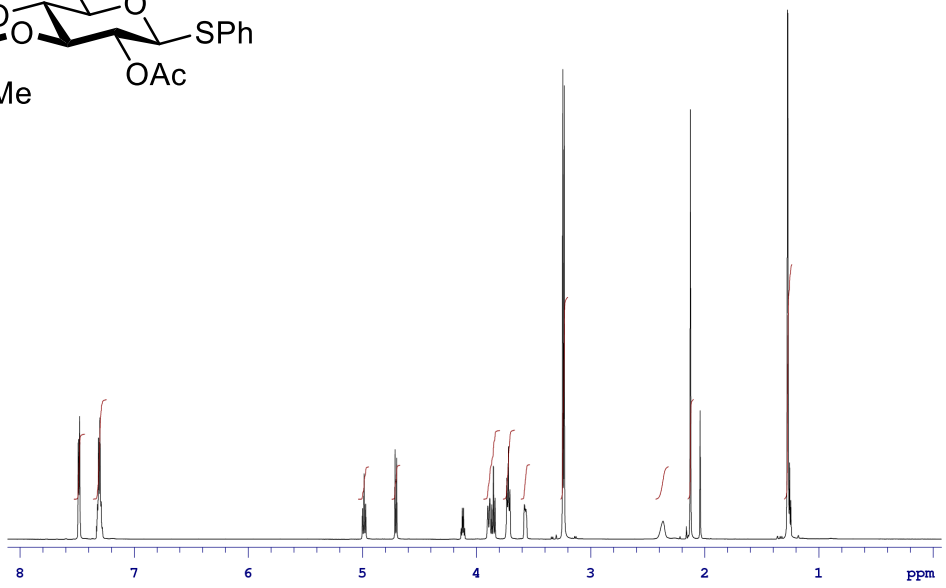
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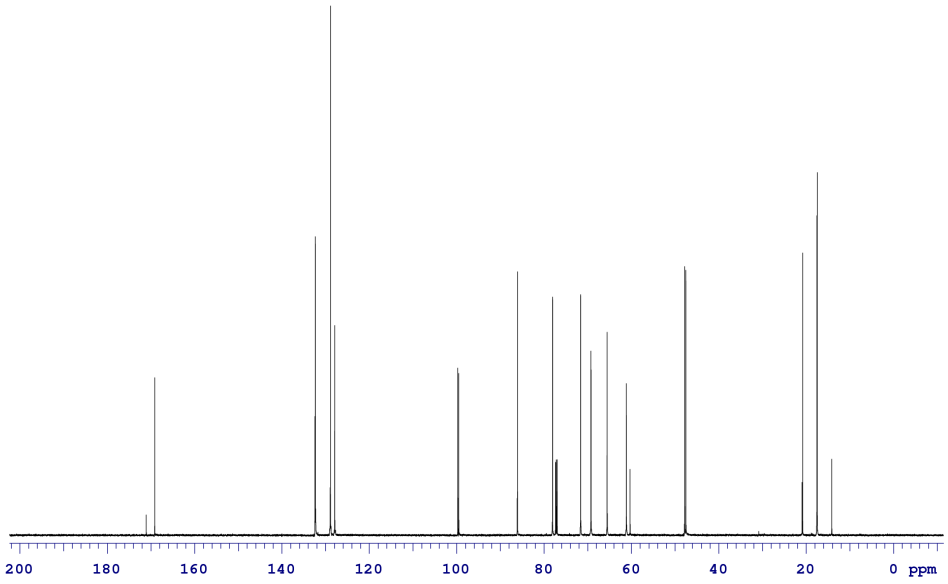
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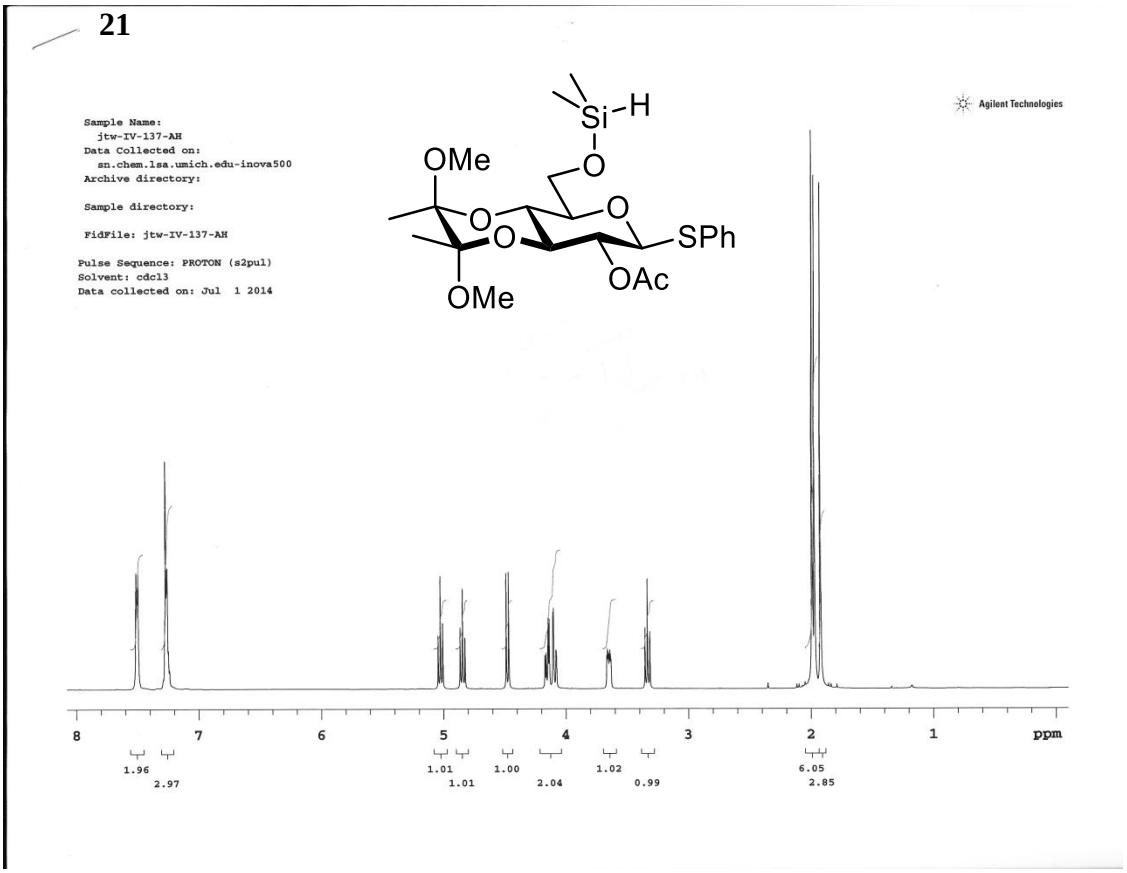
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Solvent: cdcl3
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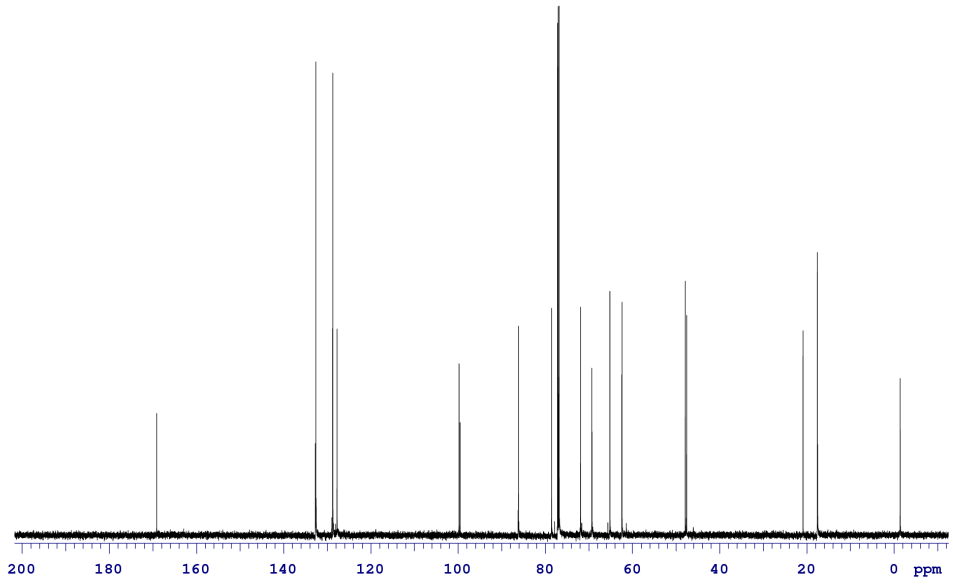
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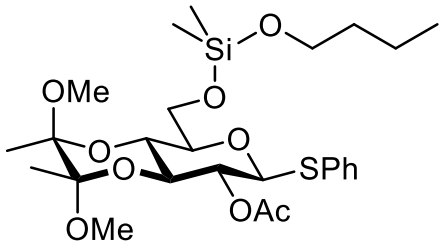
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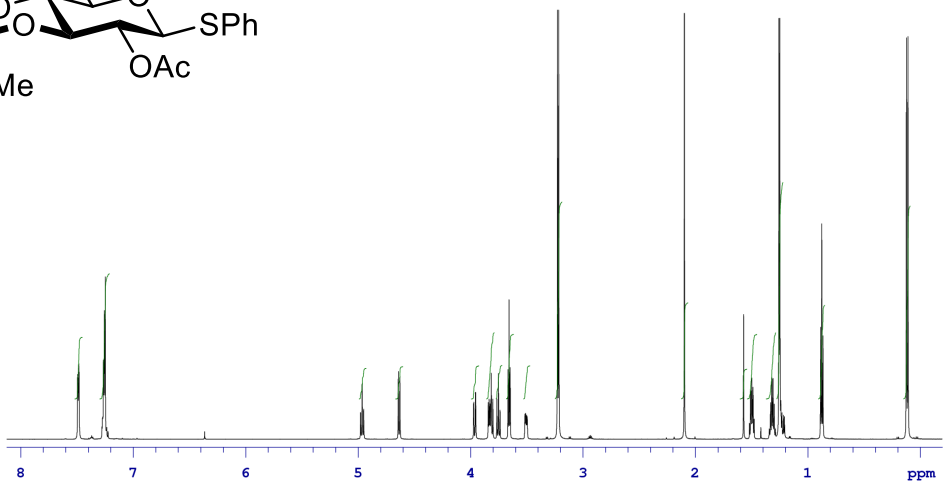
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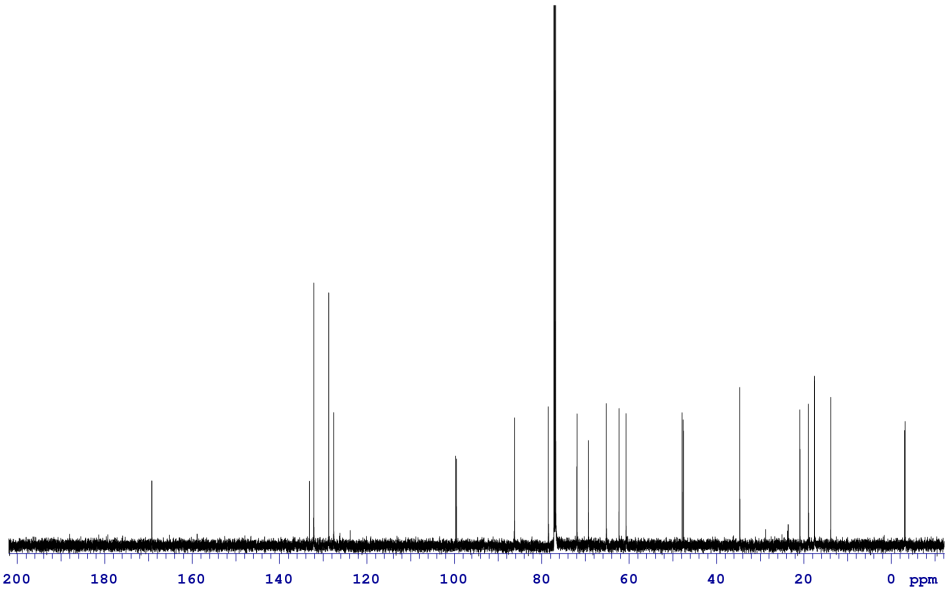
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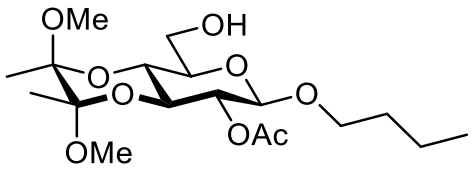
38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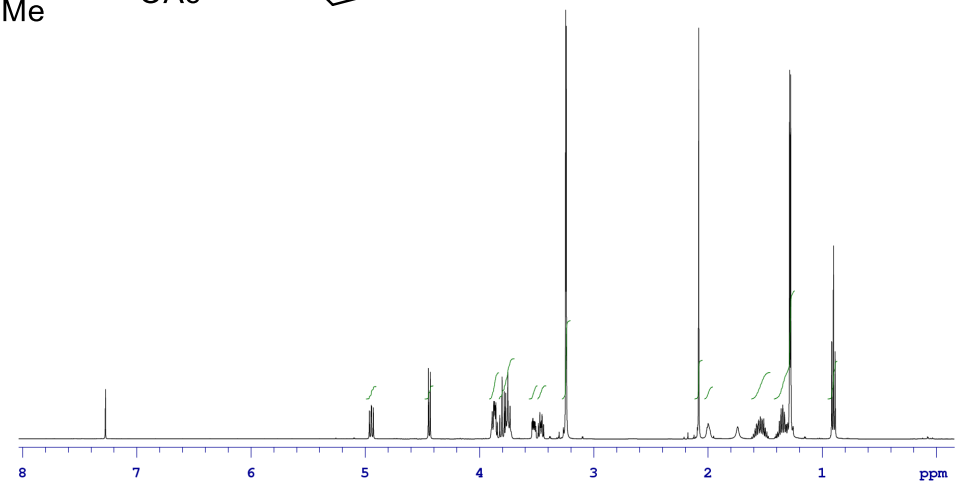
O
O
OAc
OMe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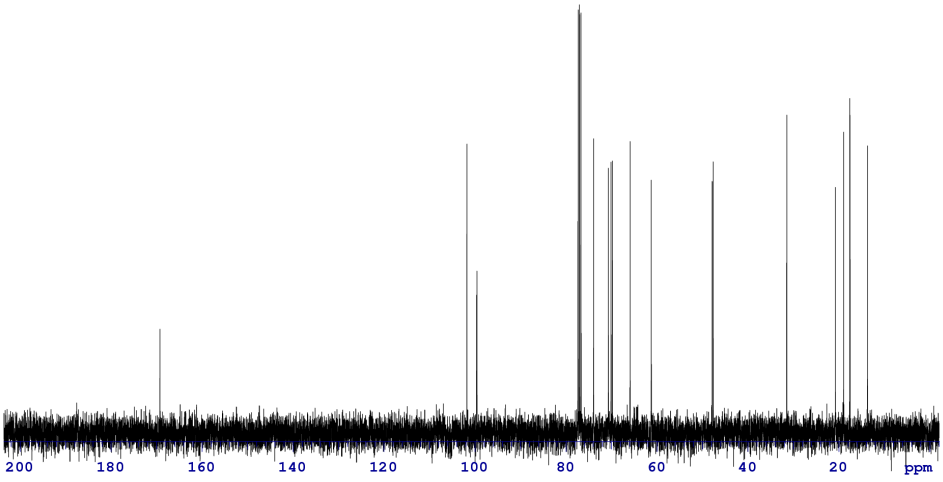
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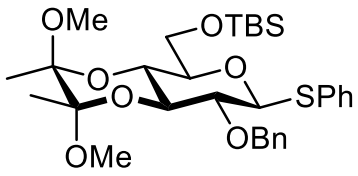
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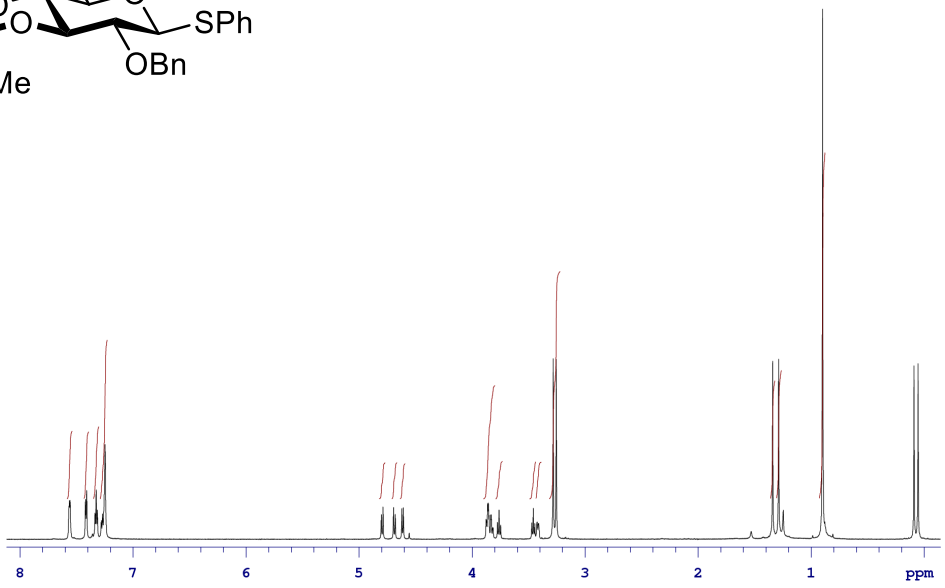
OBn
OMe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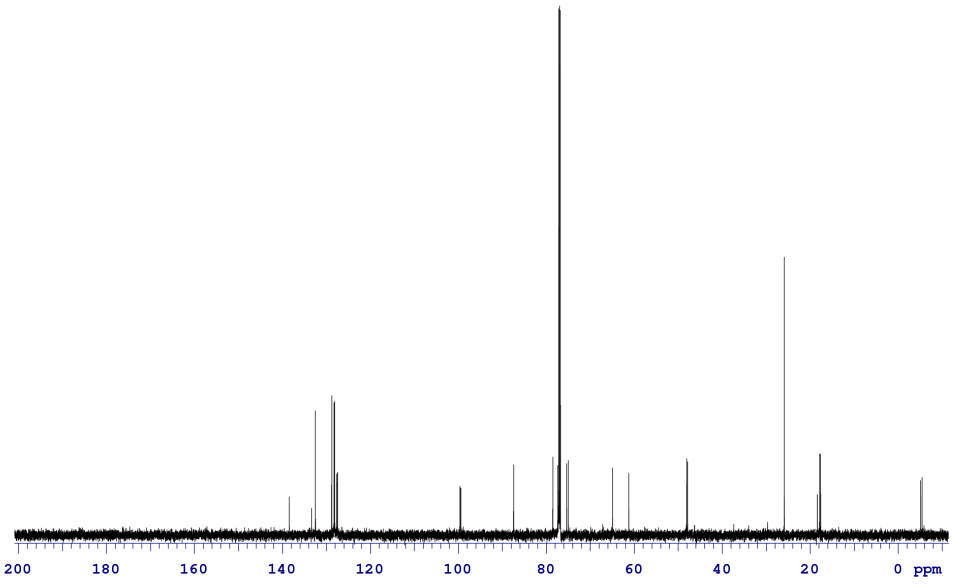
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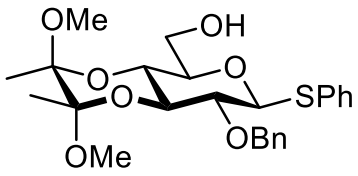
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OBn
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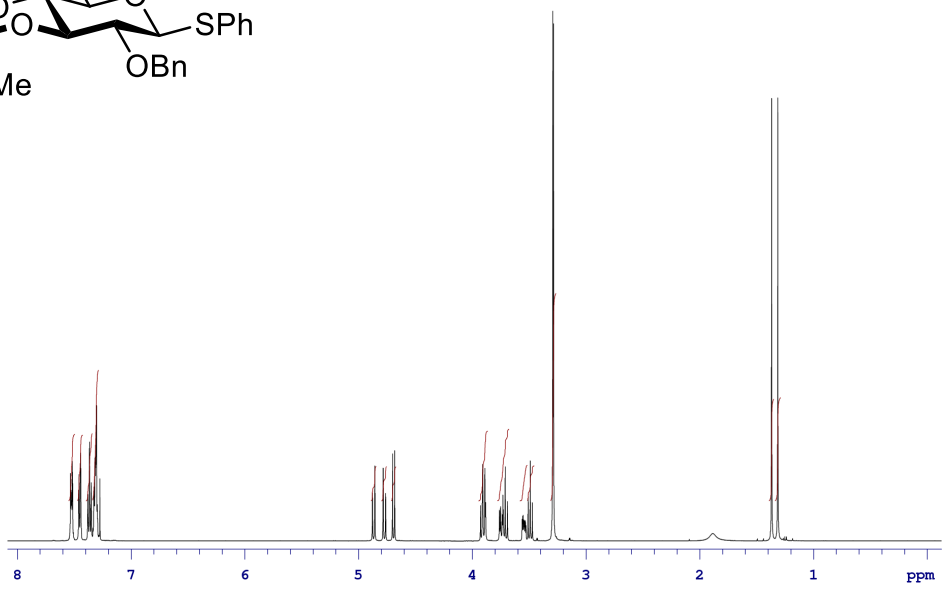
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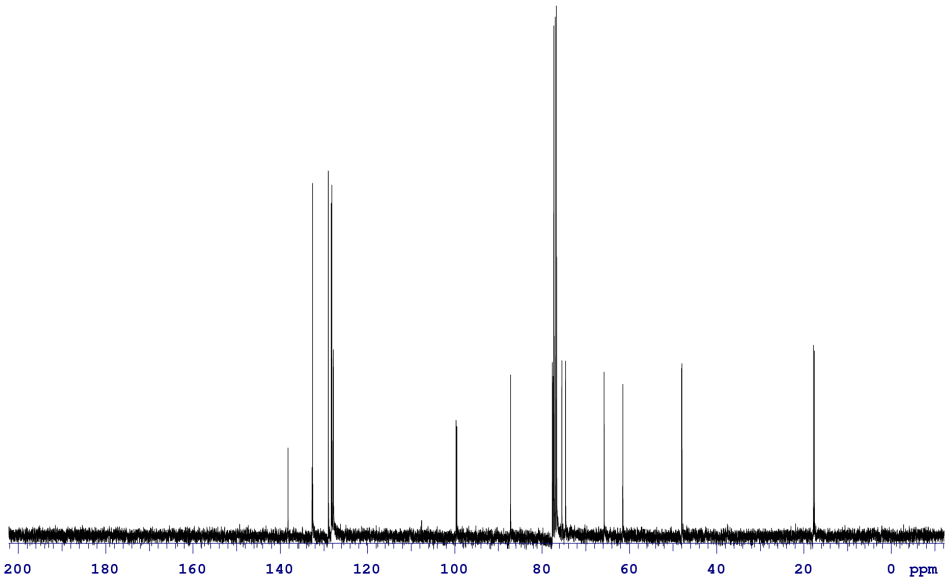
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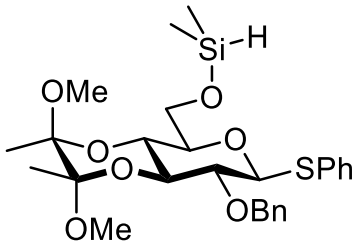
46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OMe
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O
O
SPh
OBn
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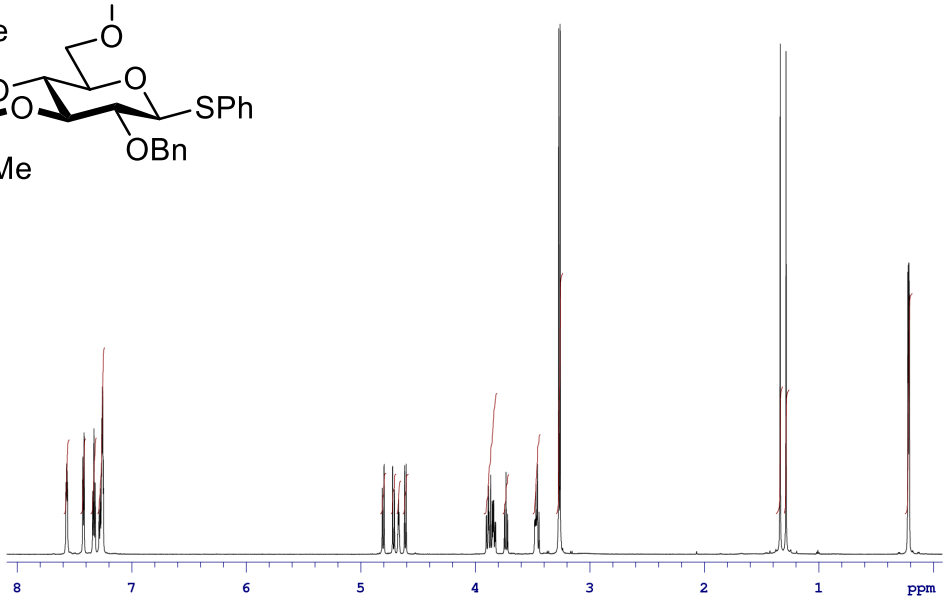
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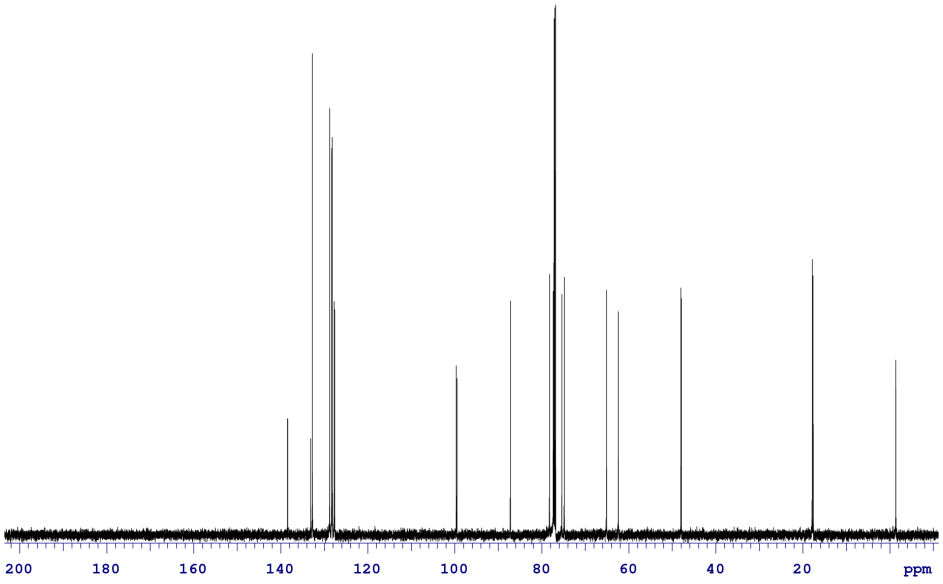
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ppm

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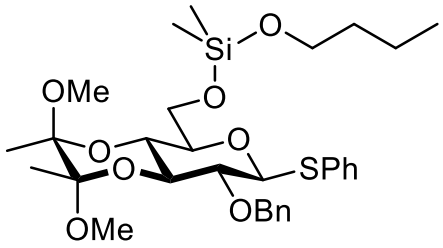
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OMe
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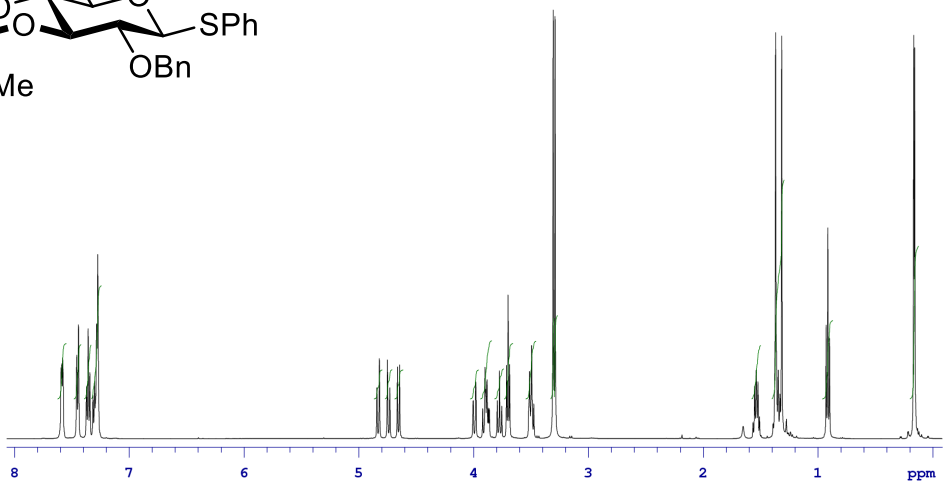
O
O
SPh
OBn
OMe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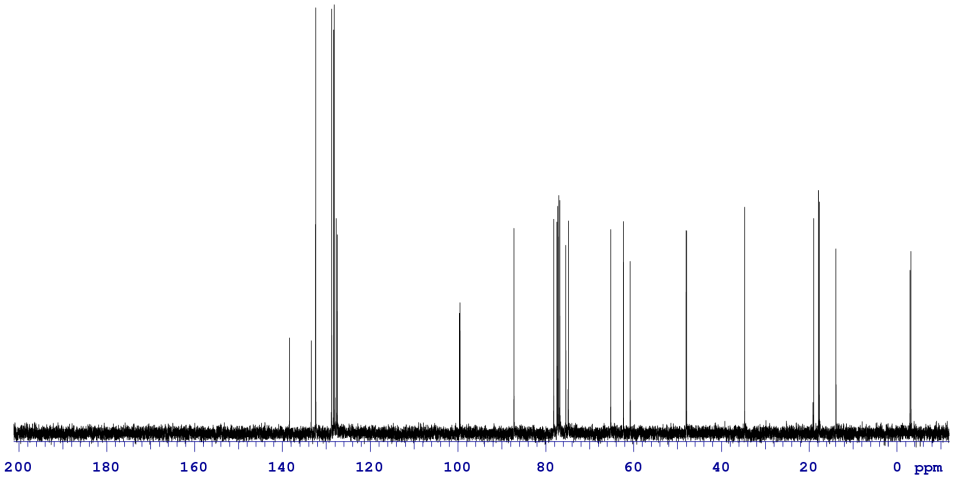
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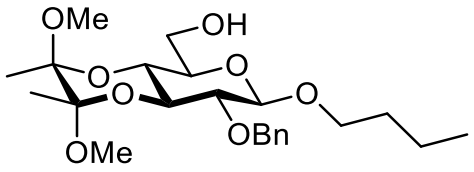
59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OH
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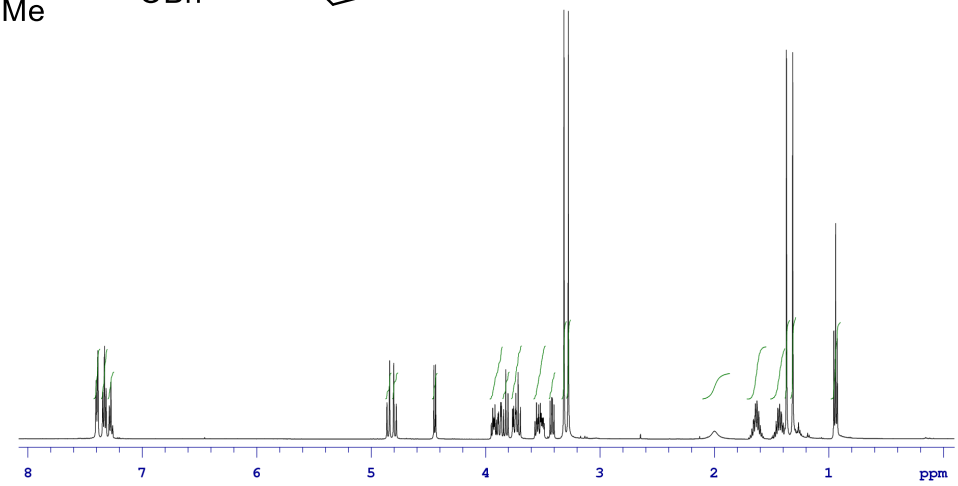
O
O
O
OBn
OMe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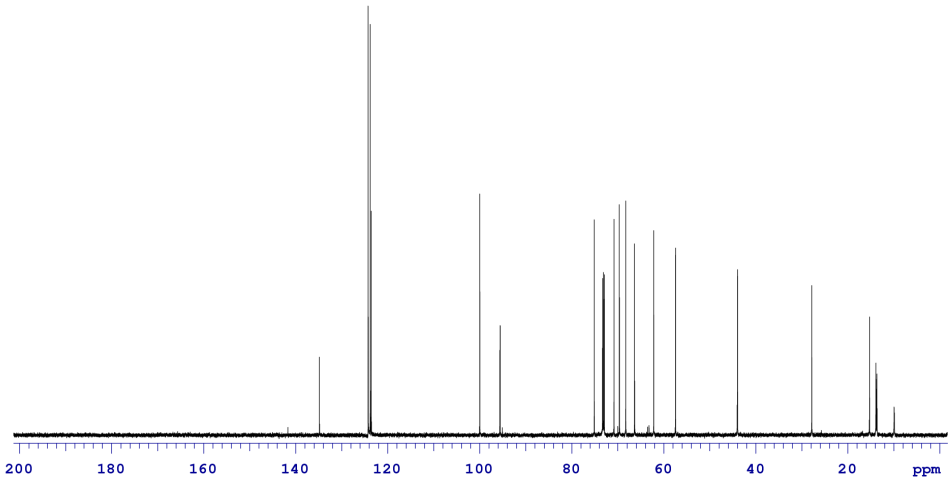
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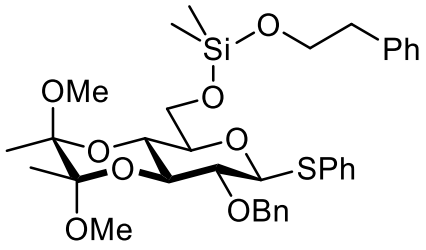
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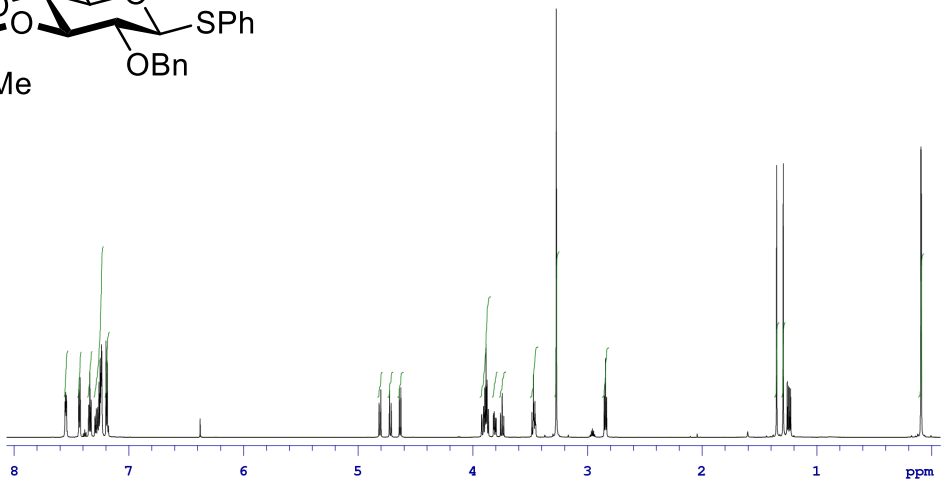
O
SPh
O
OBn
OMe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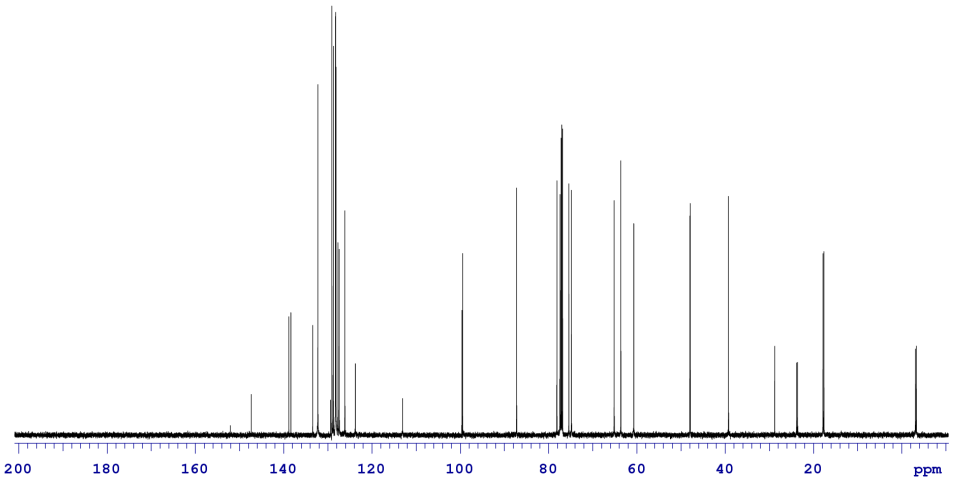
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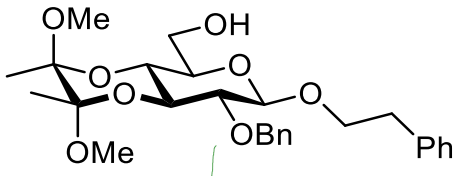
OMe
OH
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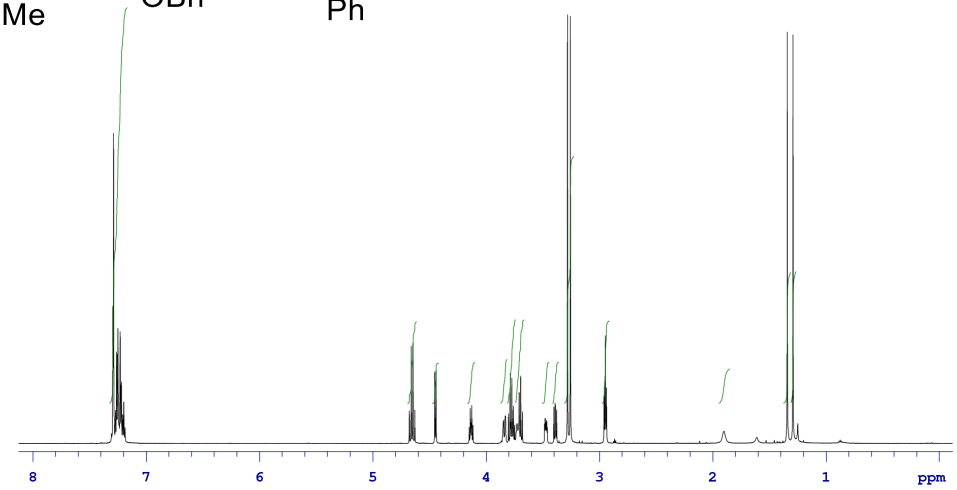
O
O
O
OBn
Ph
OMe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4
3
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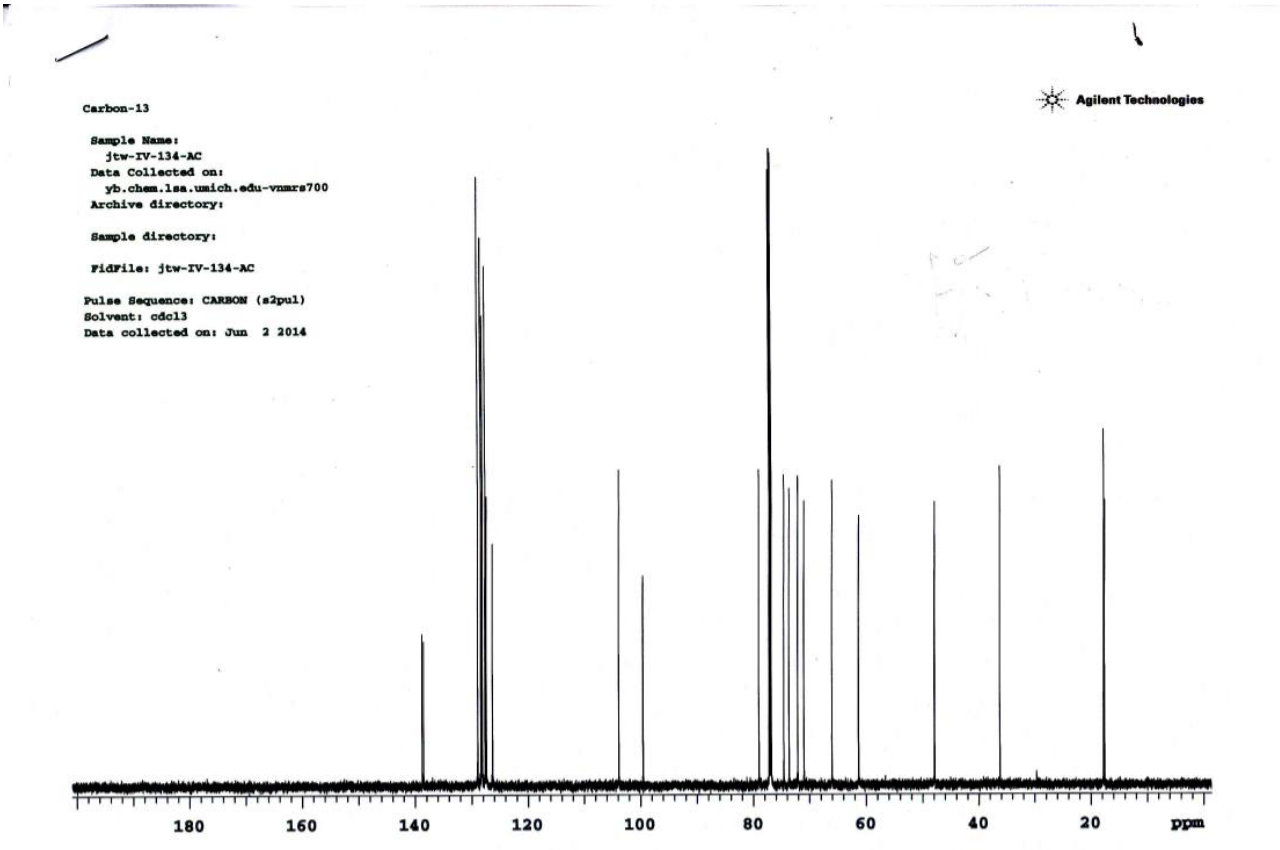
ppm


Carbon-13
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jtw-IV-134-AC
Data Collected on:
yb.chem.lsa.umich.edu-vnmrs700
Archive directory:
Sample directory:
FidFile: jtw-IV-134-AC
Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Jun 2 2014
Agilent Technologies
180
160
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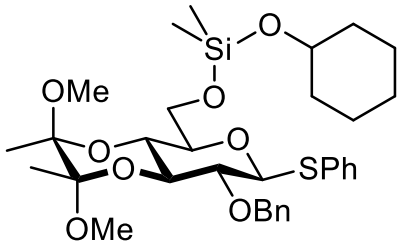
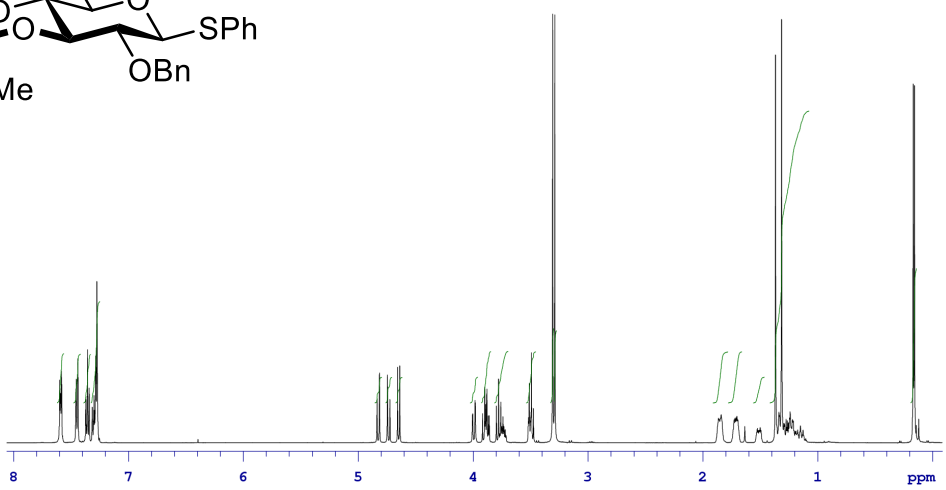
120
100
80
60
40
20
ppm

50


Si
O
OMe
O
O
O
O
SPh
OBn
OMe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5
4
3
2
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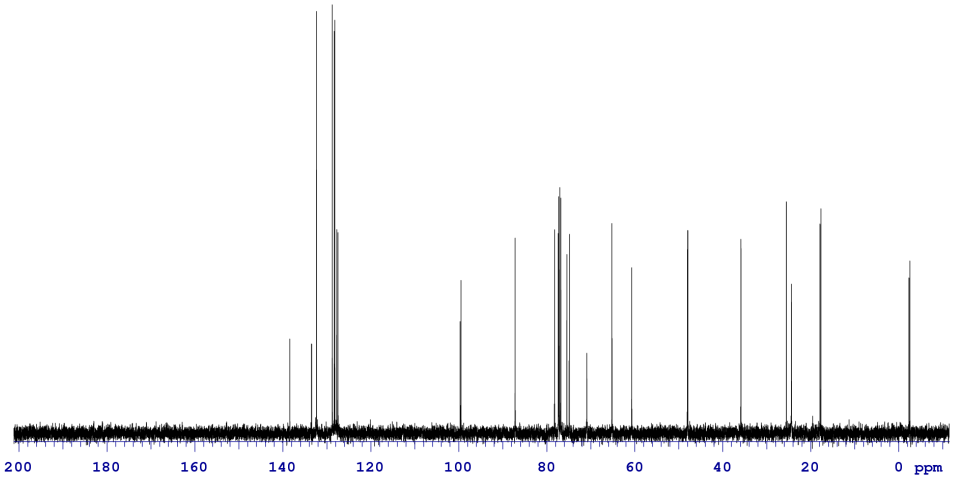
ppm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100
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60
40
20
0
ppm

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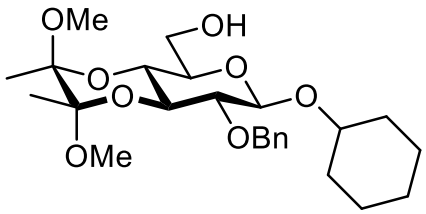
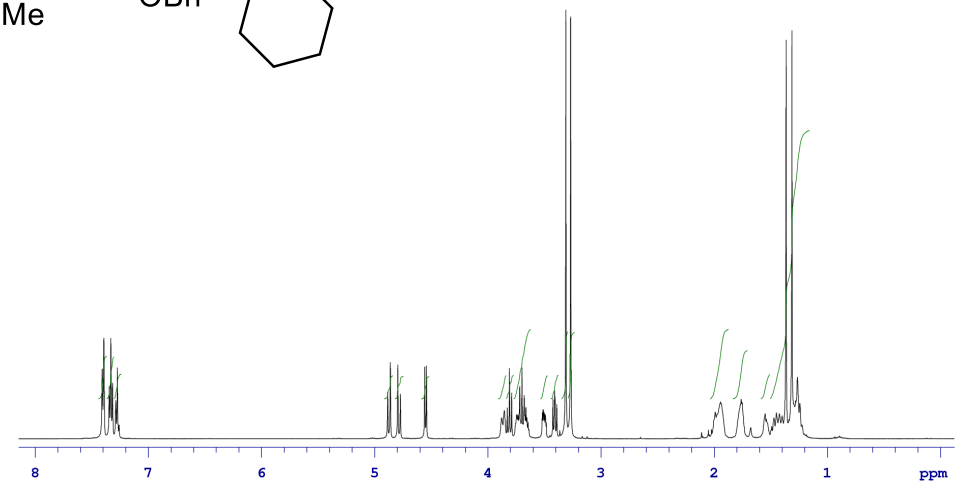

OMe
OH
O
O
O
O
OBn
OMe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6
5
4
3
2
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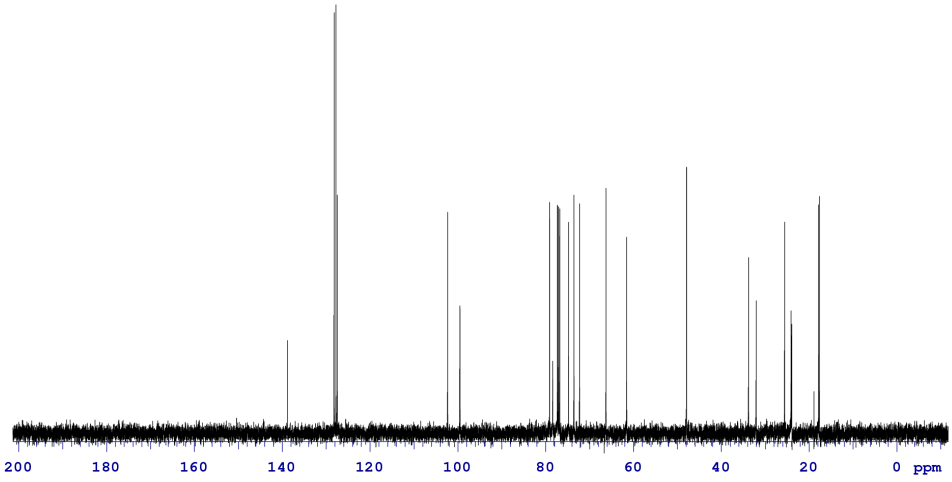
ppm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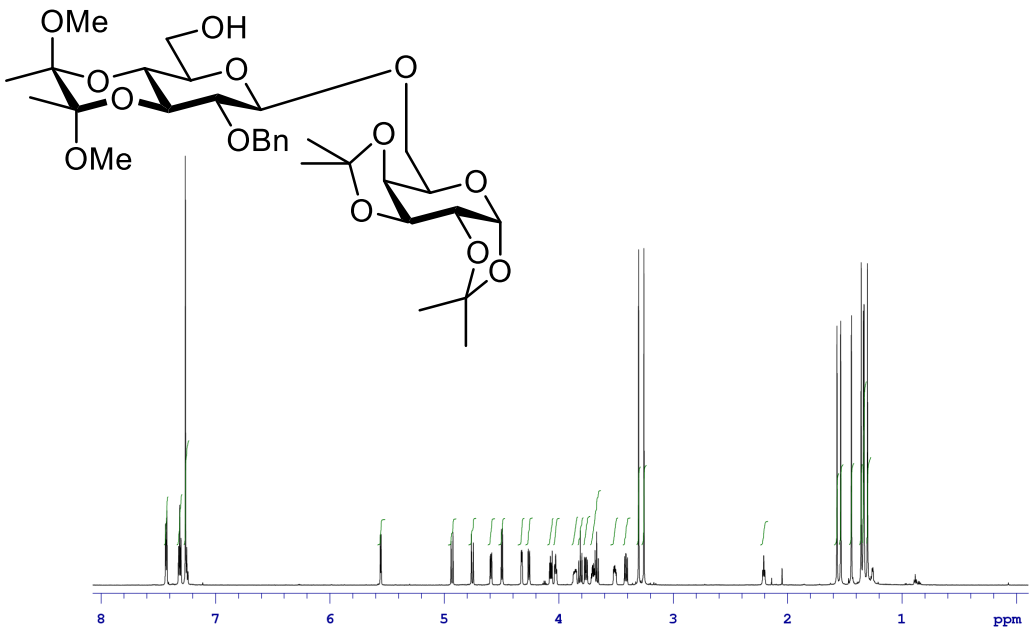
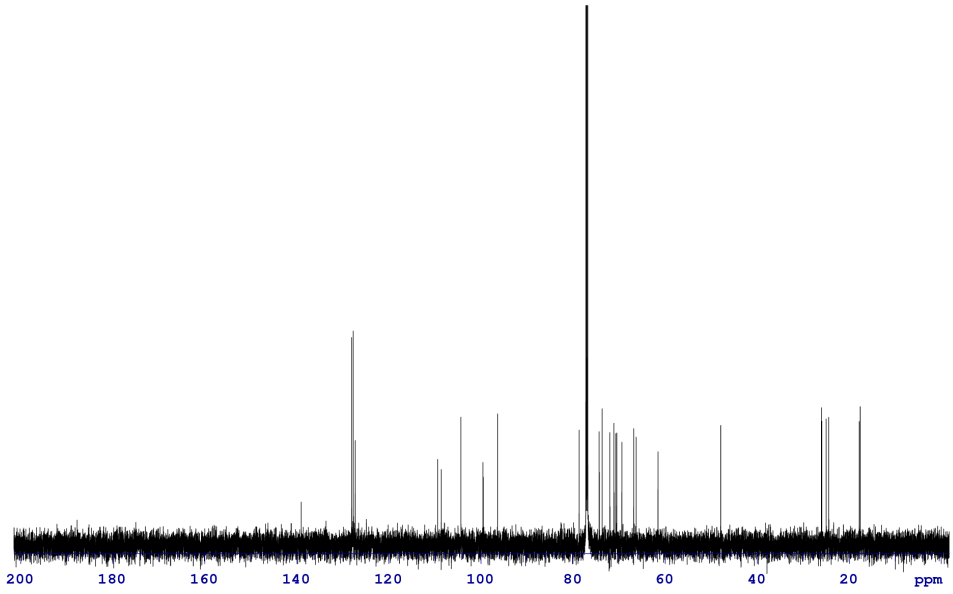
63


OMe
OH
O
O
O
O
OBn
OMe
O
O
O
O
O
8
7
6
5
4
3
2
1
ppm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120
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80
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40
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ppm

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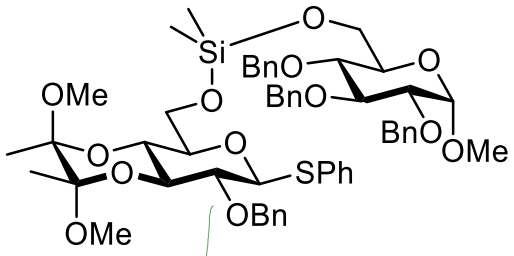
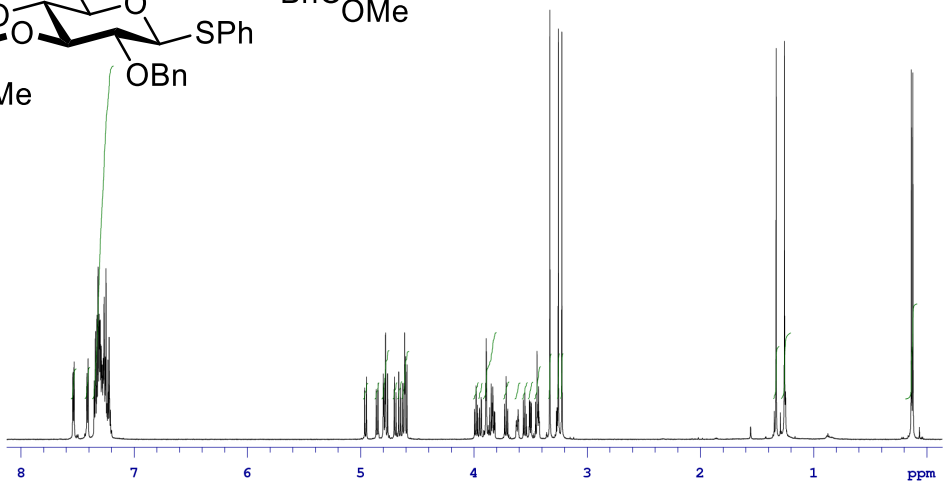

Si
O
BnO
O
BnO
BnO
OMe
OMe
O
O
O
O
SPh
OBn
OMe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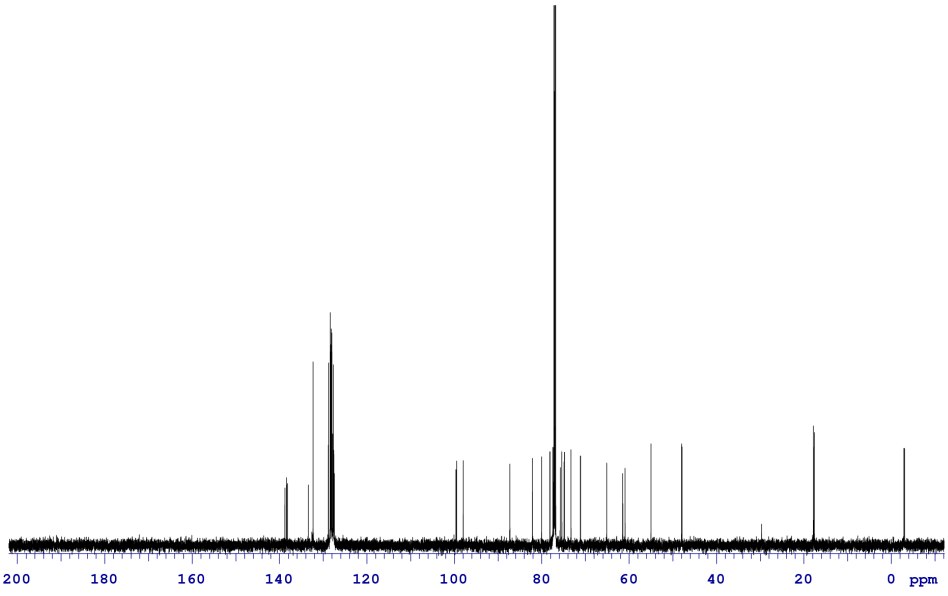
6
5
4
3
2
1
ppm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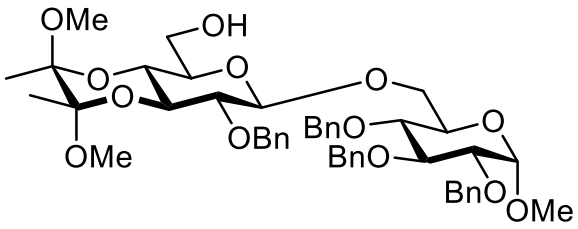
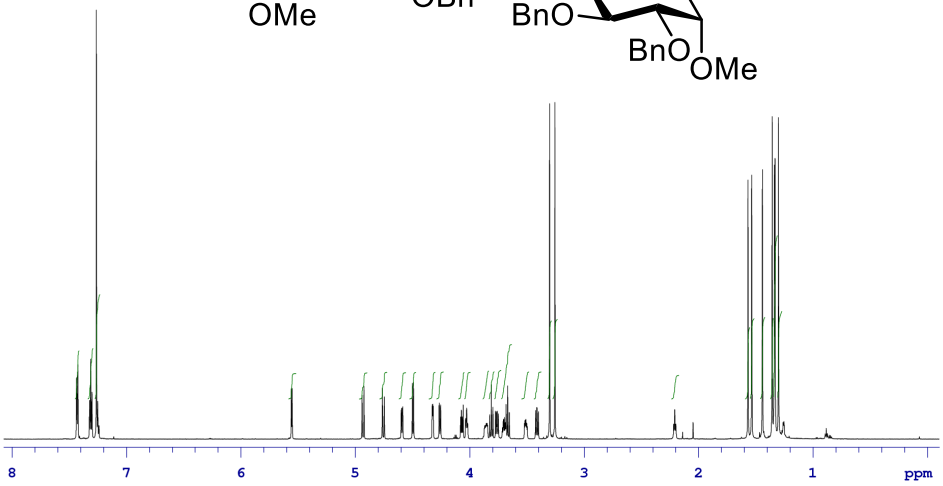
ppm

62


OMe
OH
O
O
O
O
OBn
BnO
O
BnO
BnO
OMe
OMe


8
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4
3
2
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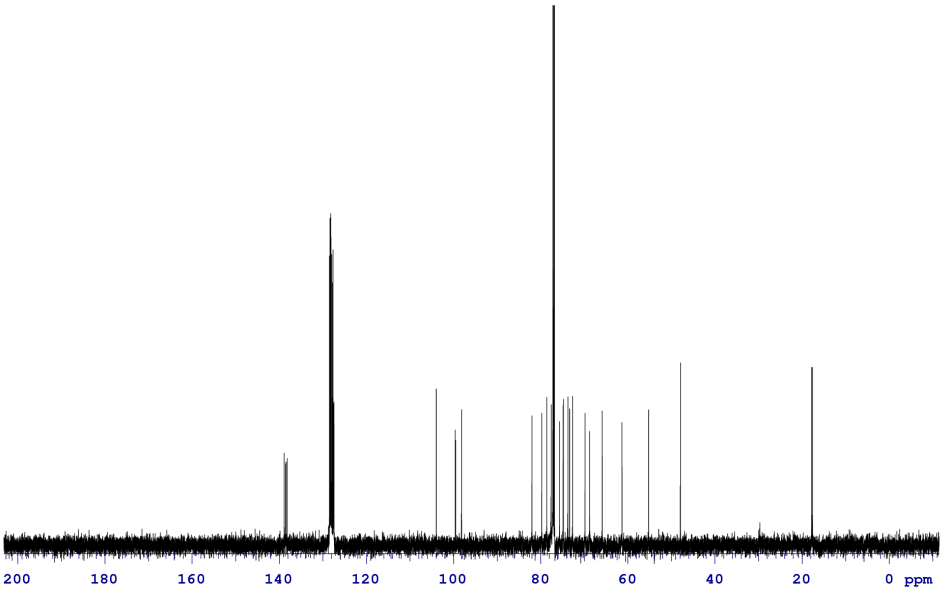
ppm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100
80
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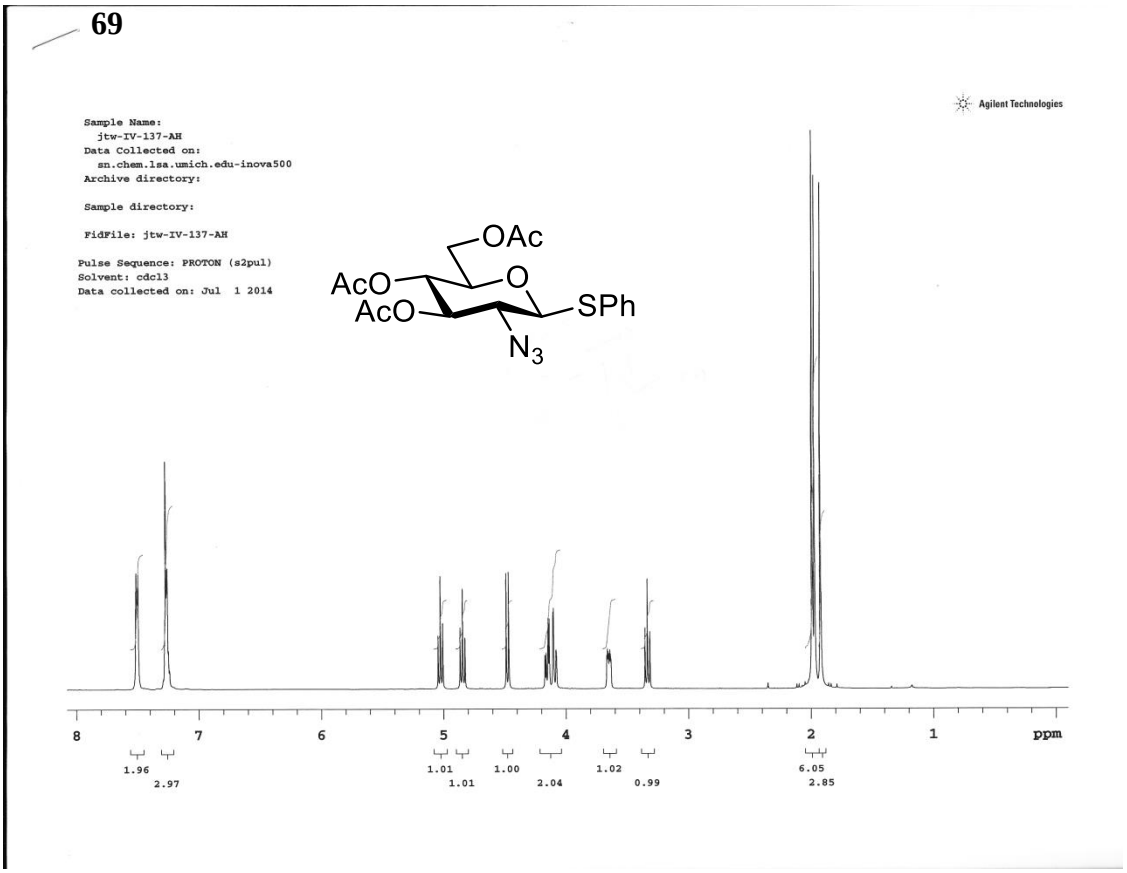
40
20
0 ppm

69


Agilent Technologies
Sample Name:
jtw-IV-137-AH
Data Collected on:
sn.chem.lsa.umich.edu-inova500
Archive directory:
Sample directory:
FidFile: jtw-IV-137-AH
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 1 2014
OAc
AcO
AcO
O
SPh
N3
8
7
6
5
4
3
2
1
ppm
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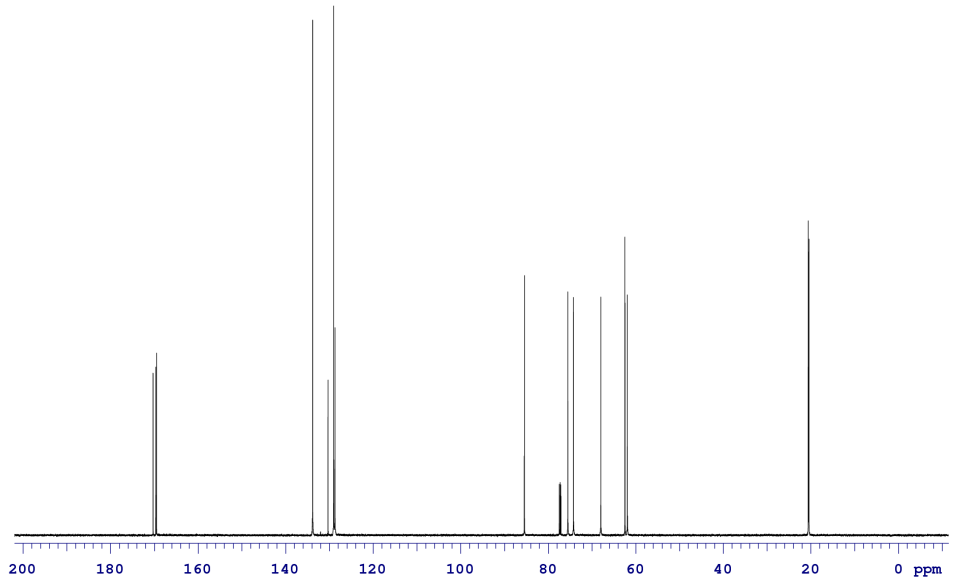
2.97
1.01
1.01
1.00
2.04
1.02
0.99
6.05
2.85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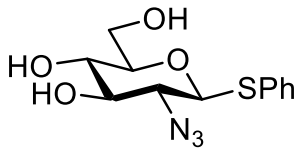
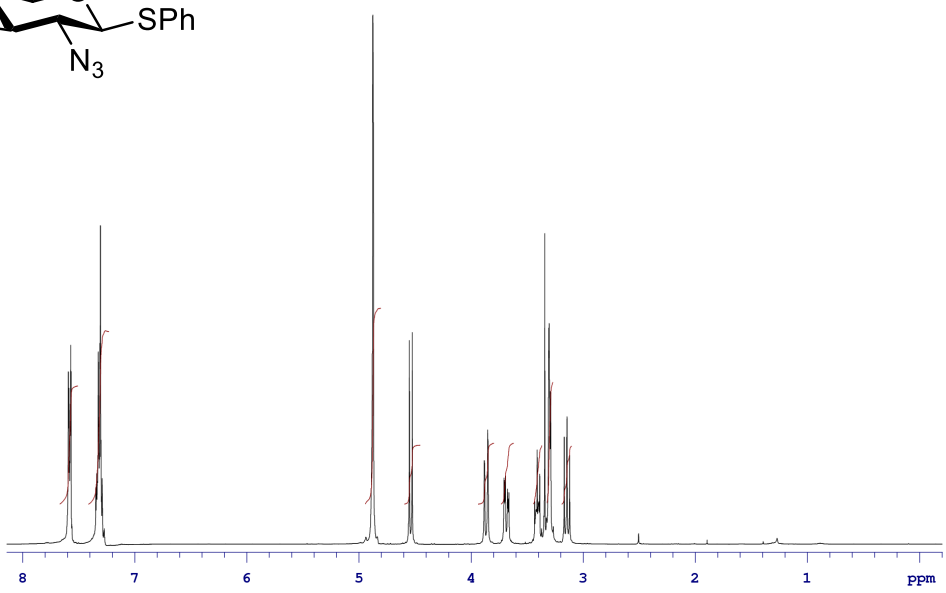
120
100
80
60
40
20
0 ppm

70


OH
HO
O
HO
SPh
N3


8
7
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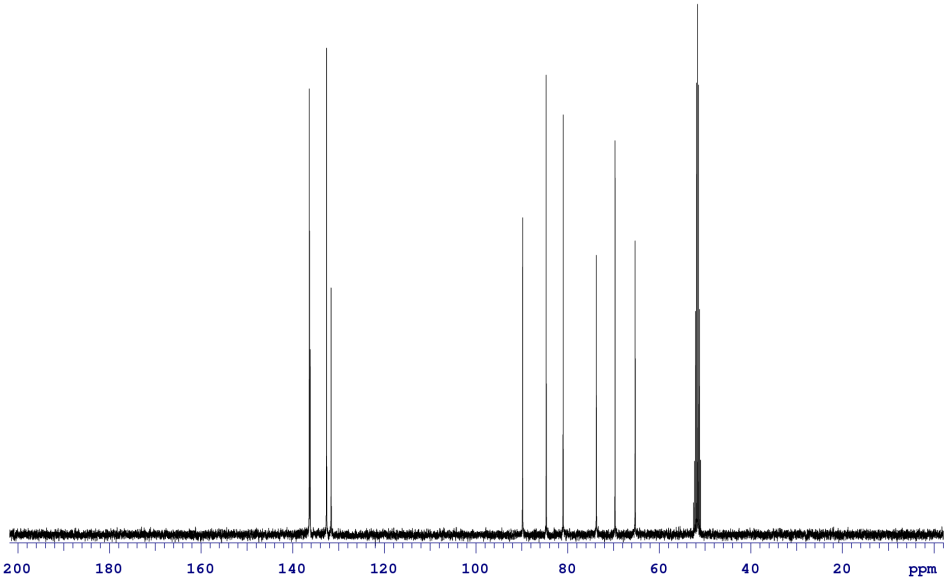
5
4
3
2
1
ppm


200
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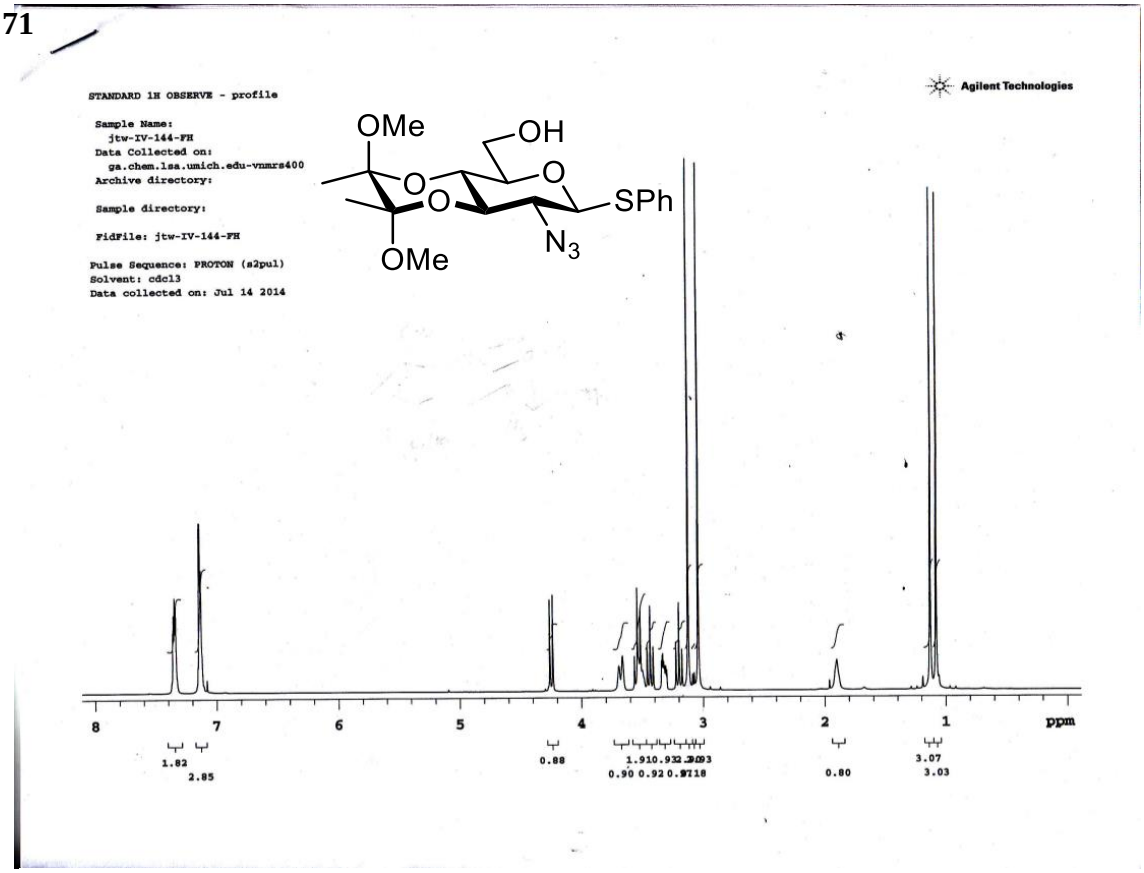
120
100
80
60
40
20
ppm

71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Data Collected on:
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Archive directory:
Sample directory:
FidFile: jtw-IV-144-FH
Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: Jul 14 2014
Agilent Technologies
OMe
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O
O
SPh
N3
OMe
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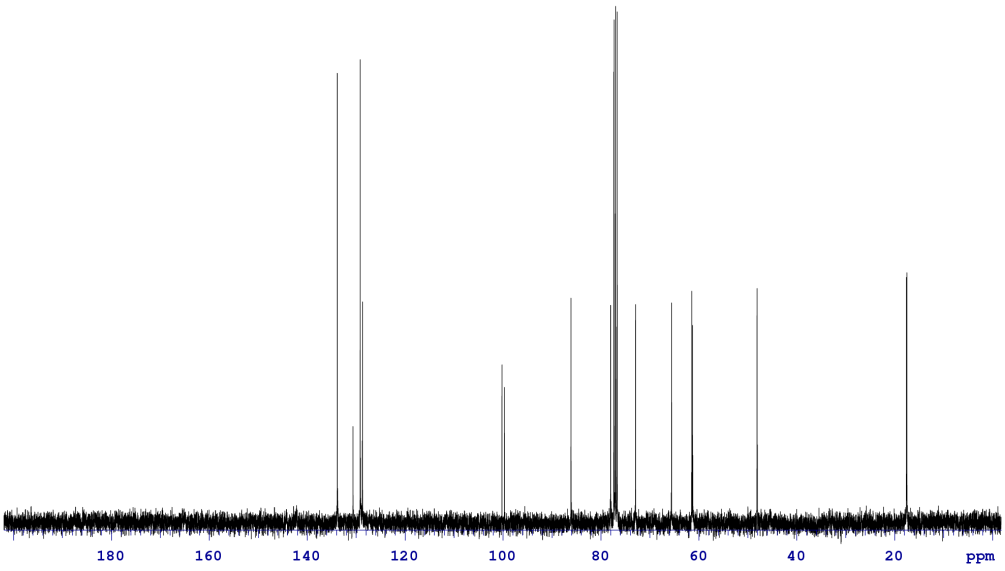
3.03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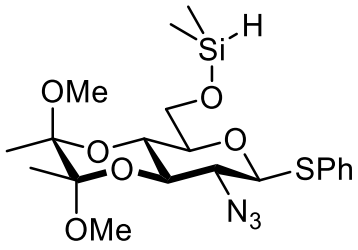
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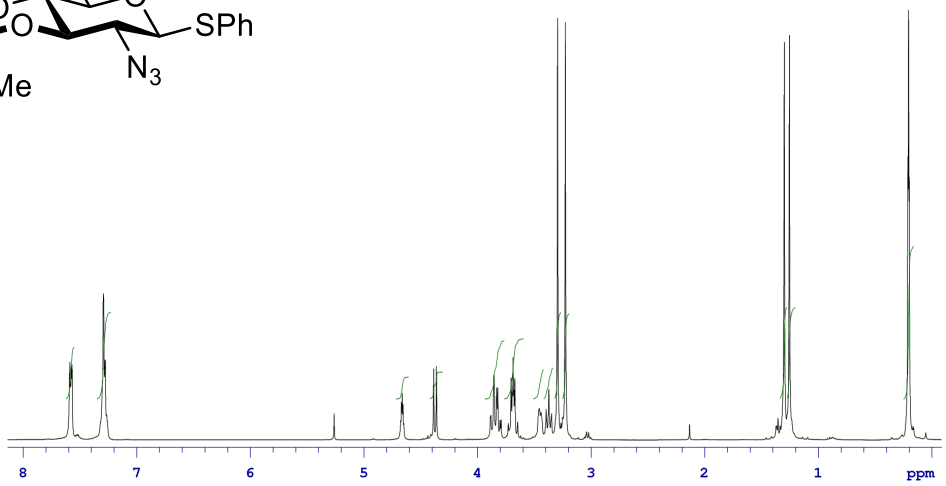
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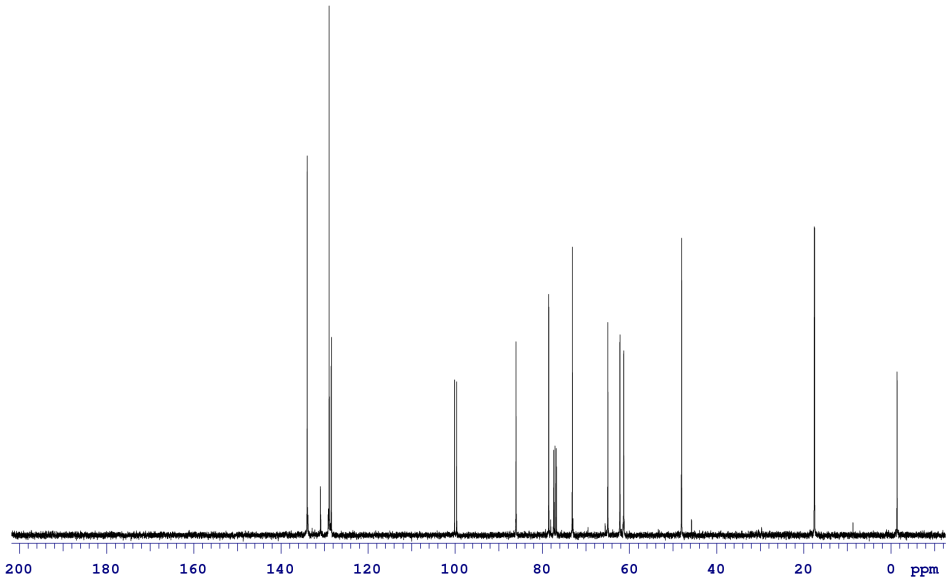
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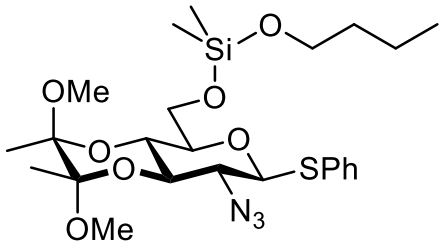
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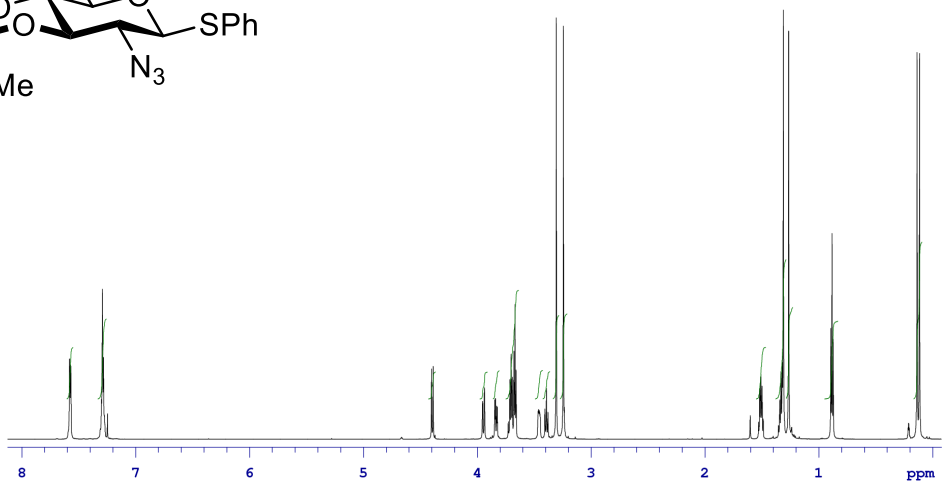
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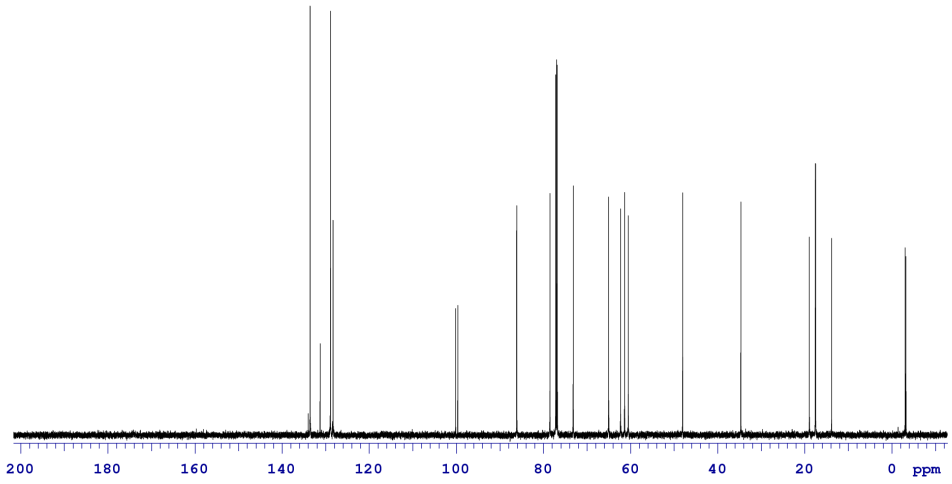
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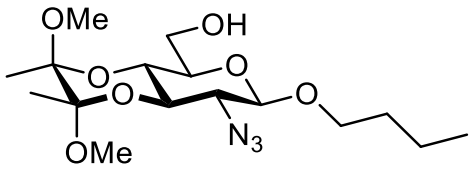
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N3
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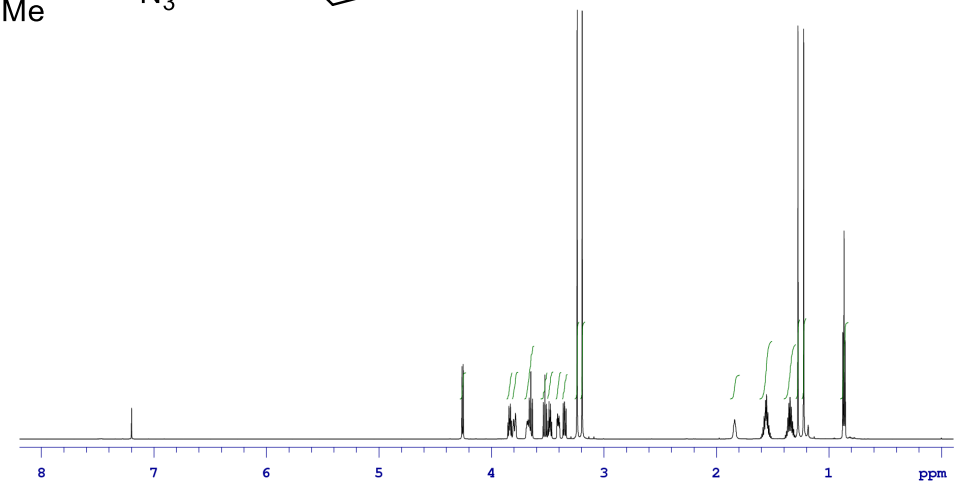
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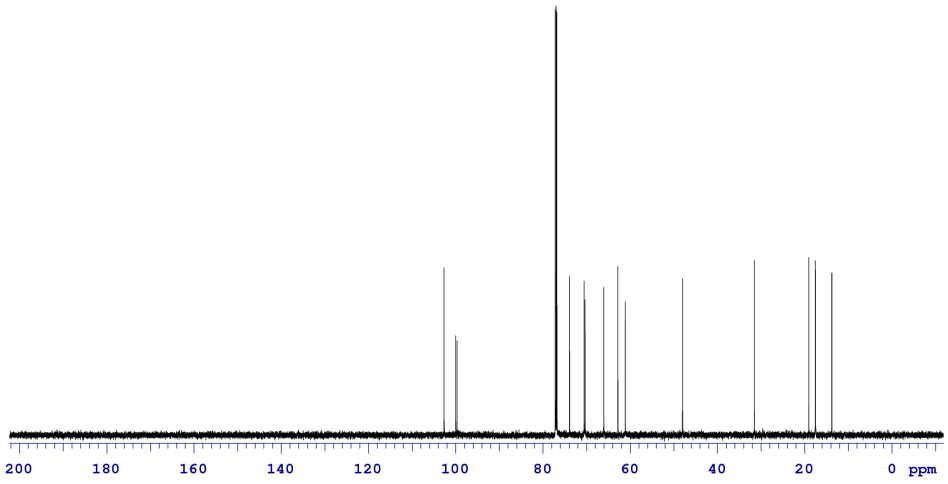
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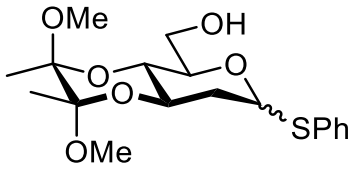
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SPh
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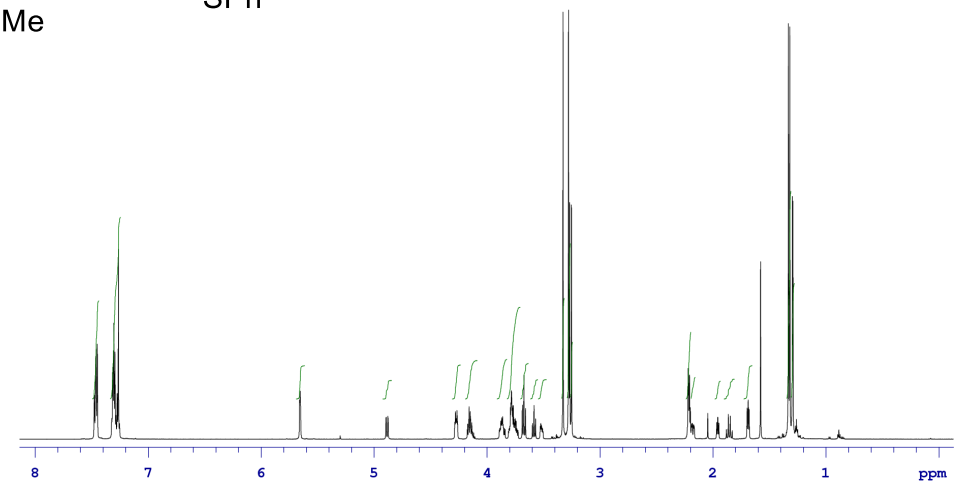
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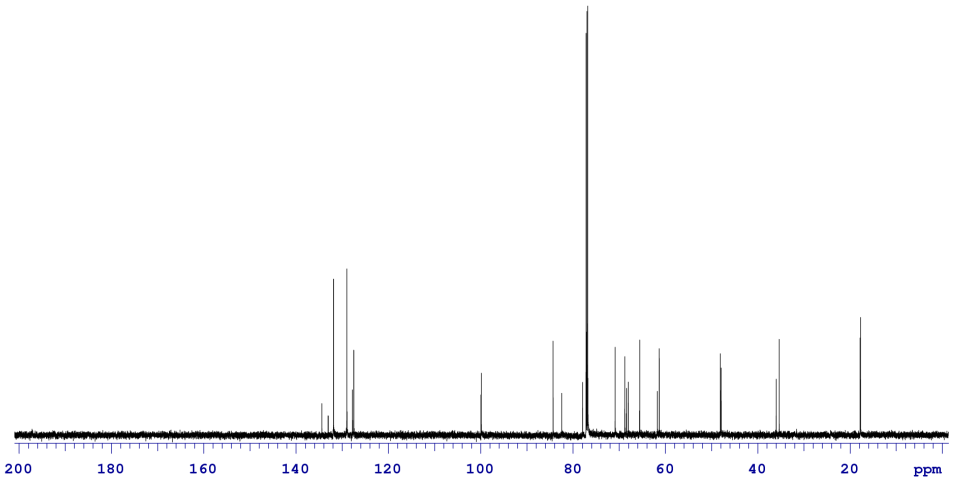
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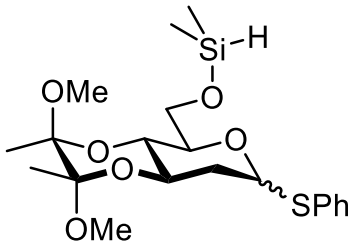
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O
O
SPh
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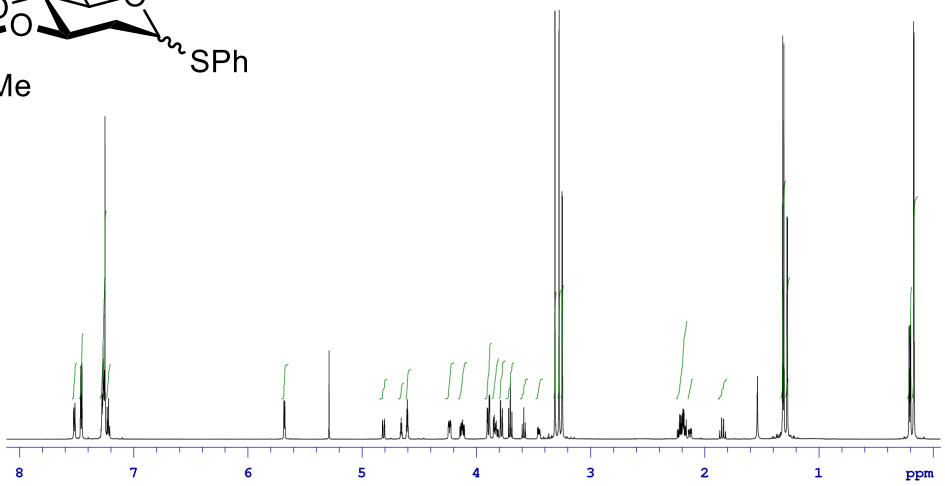
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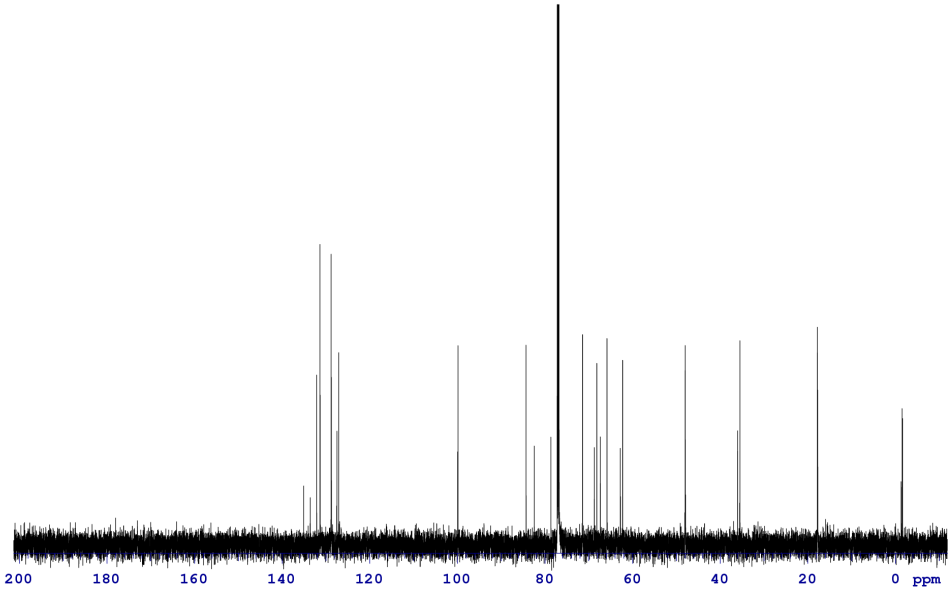
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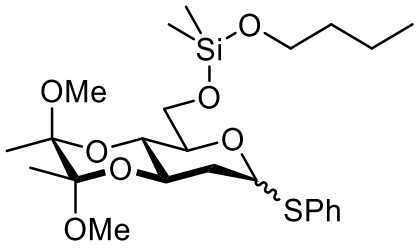
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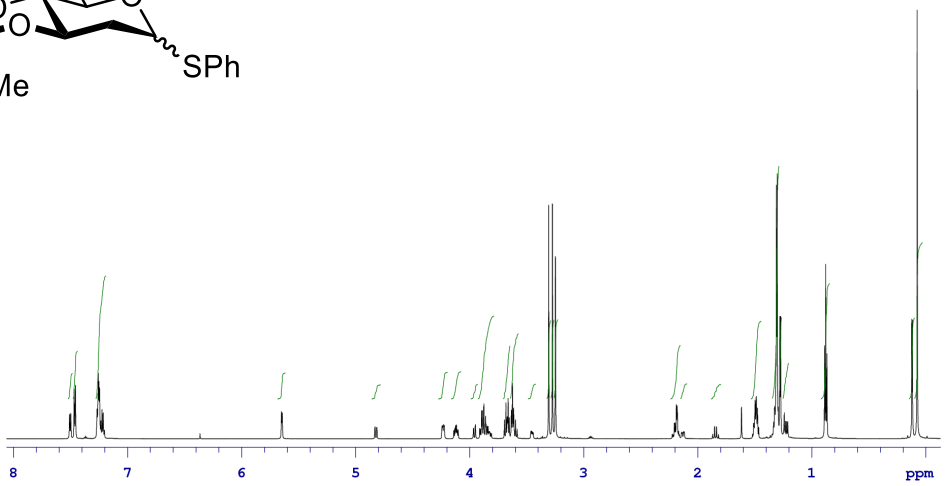
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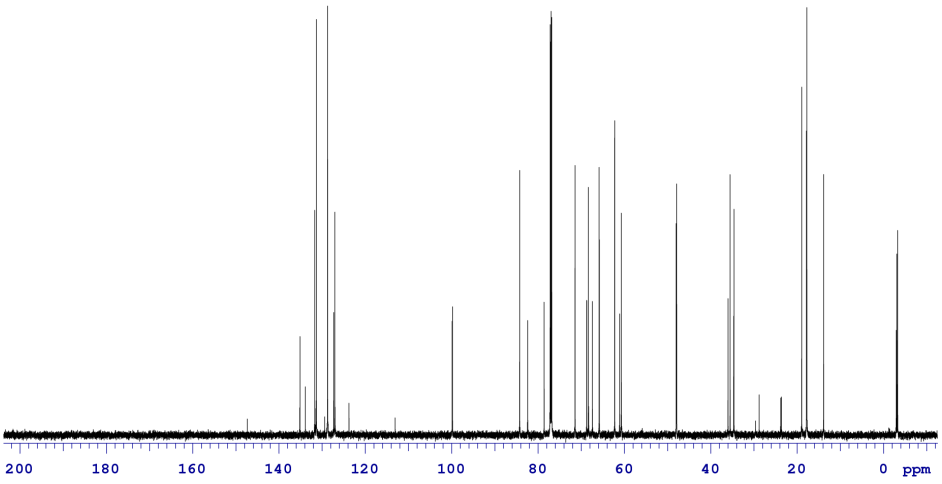
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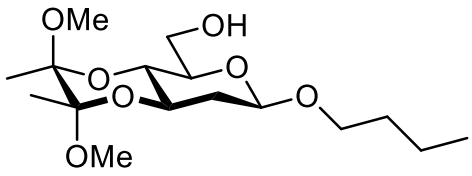
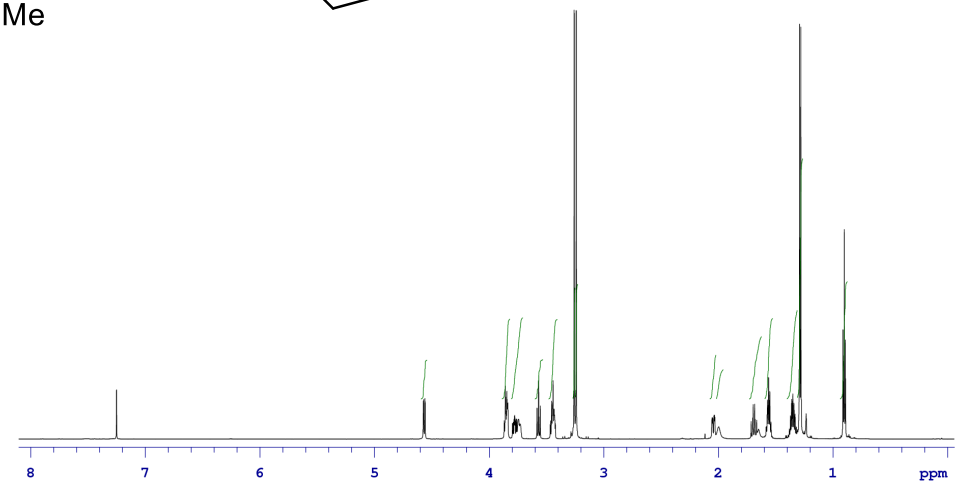
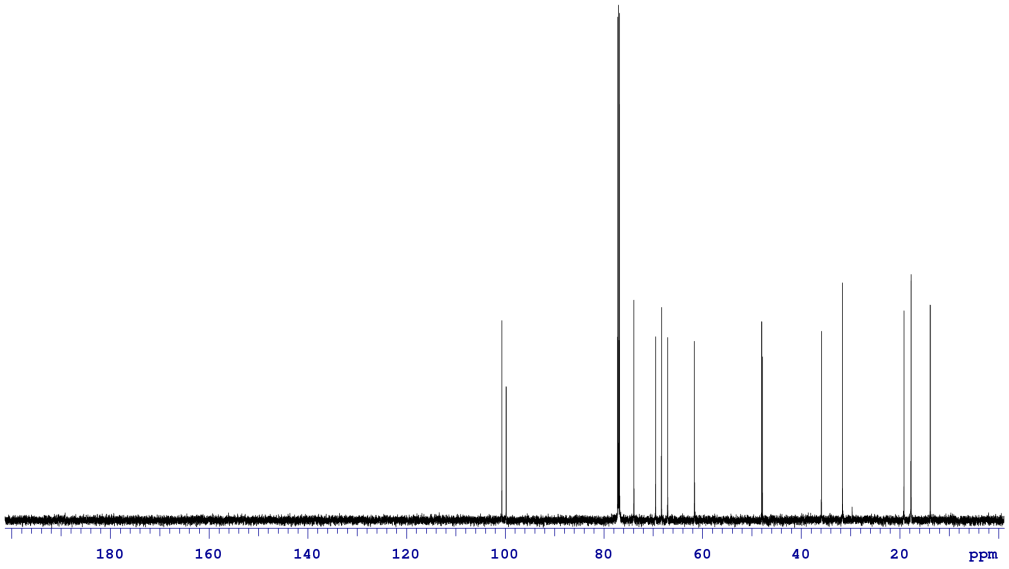
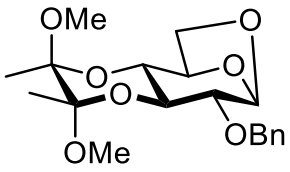
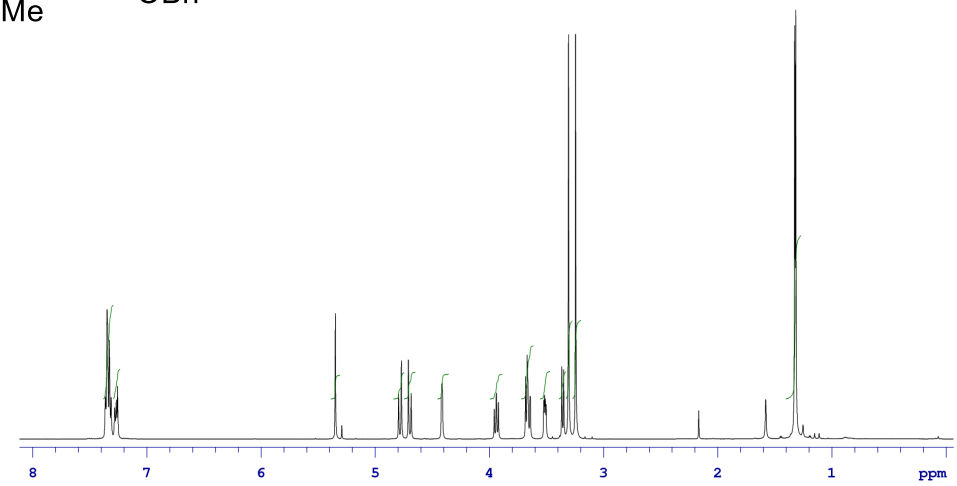


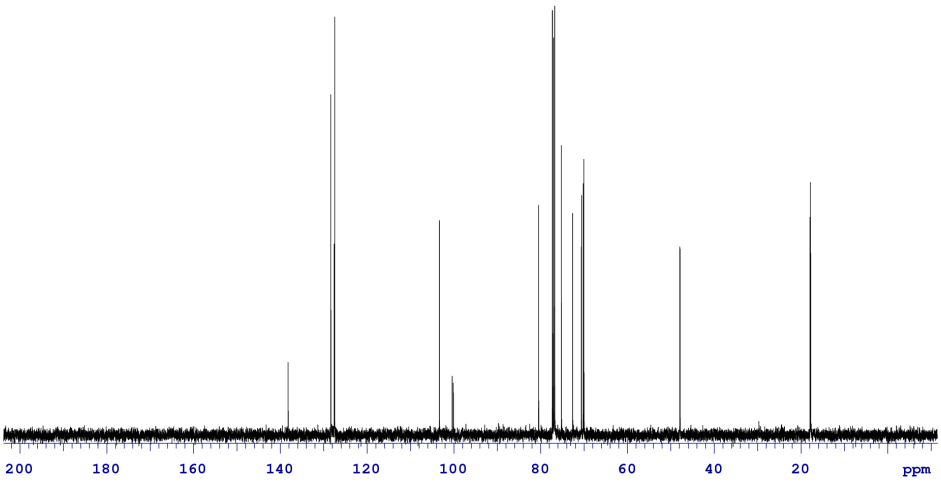




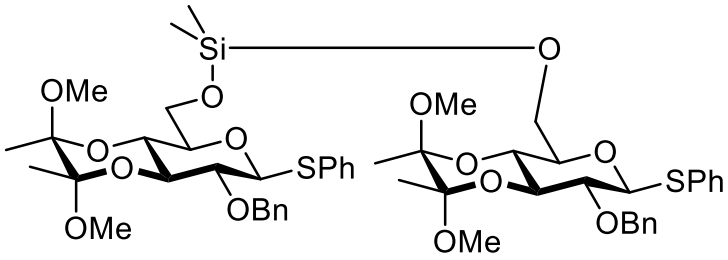
1,6-Anhydro Byproduct







Homodimer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O
O
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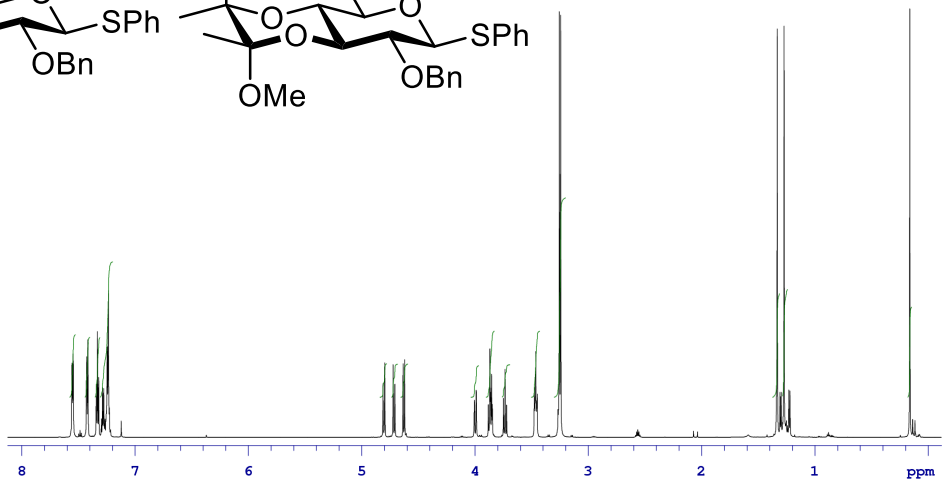
OMe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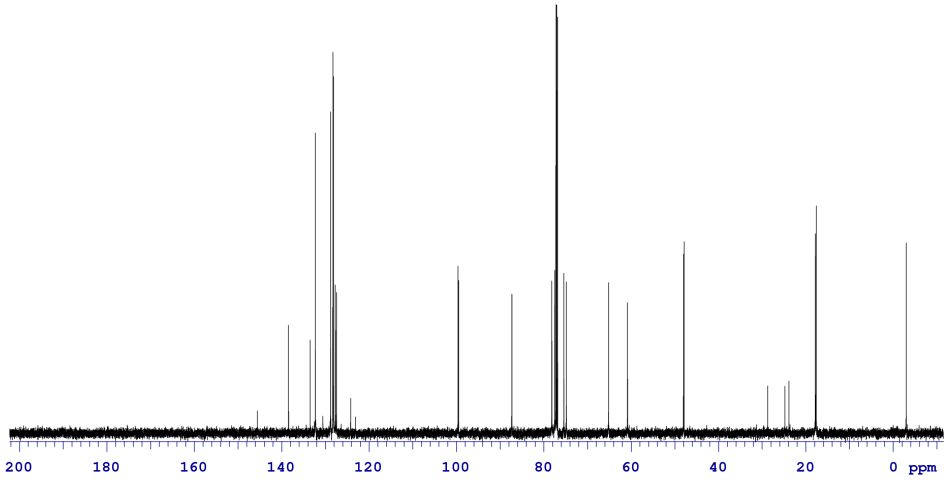
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References

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